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CITATIONS

In the Supreme Court of the United States

OCTOBER TERM, 1972

No.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, PETITIONERS

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

The Solicitor General, on behalf of the Secretary of Health, Education, and Welfare and the Commissioner of Food and Drugs, petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Fourth Circuit in this case.

OPINIONS BELOW

The opinion of the court of appeals (App. A, *infra*, pp. 1a–11a) is not yet officially reported. The order of the Commissioner of Food and Drugs was published in the Federal Register on June 18, 1971 (36 Fed. Reg. 11763) (App. C, *infra*, pp. 14a–22a).

JURISDICTION

The judgment of the court of appeals was entered on May 24, 1972 (App. B, *infra*, pp. 12a–13a). Mr. Justice Rehnquist extended the time within which to file a petition for certiorari to September 7, 1972. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1) and 21 U.S.C. 355(h).

QUESTIONS PRESENTED

Whether the Commissioner of Food and Drugs may, in implementing the drug effectiveness requirements of the 1962 amendments to the Food, Drug, and Cosmetic Act of 1938, withdraw approval for the marketing of a drug for lack of proof of effectiveness without a hearing, if the manufacturer has failed to comply with the Commissioner's regulations requiring that a request for hearing must be supported by the kind of "substantial evidence" of effectiveness required by the statute.

STATUTORY PROVISIONS AND REGULATIONS INVOLVED

Section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) provides in pertinent part:

> The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds * * * (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug

> will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof * * *.

Section 505(d) (21 U.S.C. 355(d)) provides in pertinent part:

> * * * As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof.

Pertinent provisions of the regulations of the Commissioner of Food and Drugs, 21 C.F.R. 130.12(a)(5) and 130.14, as amended, 35 Fed. Reg. 7251, 7252, are set forth in Appendix D, *infra*, pp. 23a–28a.

STATEMENT

1. *Background.* This case arises out of efforts by the United States Food and Drug Administration (FDA) to insure that all drugs available to the public are effective for their intended uses. Prior to 1962, the Federal Food, Drug, and Cosmetic Act of 1938, 52 Stat. 1052, required only that the sponsor of a new drug provide evidence that the product was safe for its intended uses in order to obtain FDA approval for

marketing. This was one of the major deficiencies in the Act which Congress sought to remedy in the Harris-Kefauver Drug Amendments of 1962, 76 Stat. 781. Section 201(p) of the Act was amended to define a "new drug" as one not generally recognized by qualified experts as safe *and effective* for its intended uses (21 U.S.C. 321(p)(1)). Under Section 505(e) (21 U.S.C. 355(e)), the agency was given authority to withdraw approval of new drug applications (NDAs) previously granted if the NDA holder cannot provide "substantial evidence" of the drug's effectiveness. "Substantial evidence" is defined in the statute to mean "adequate and well controlled investigations, including clinical investigations" by scientific experts, on the basis of which effectiveness could be determined (Section 505(d)). Transitional provisions in the 1962 amendments provided that holders of previously approved NDAs would not be required to produce proof of effectiveness for two years (P.L. 81-781, Section 107(c)(3)(B), 76 Stat. 788-789). This "grace period" was intended to permit drug manufacturers to undertake necessary clinical investigations to develop evidence of effectiveness, which they had not previously been required to have.[1]

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[1] The amendments also afforded an exemption from the effectiveness requirement for drugs which were commercially marketed on the enactment date, which were not covered by an effective NDA, and which were not "new drugs" as defined by the Act prior to amendment. P.L. 87-781, Section 107(c)(4), 76 Stat. 789. Respondent's claim to an exemption under this "grandfather clause" was rejected below by both the Commissioner (App. C, *infra*, p. 17a) and the court of appeals (App. A, *infra*, p. 6a).

To assist FDA in the enormous task of reviewing efficacy claims for all drugs approved between 1938 and 1962, the Commissioner of Food and Drugs, in 1966, contracted with the National Academy of Sciences-National Research Council (NAS–NRC) to establish expert panels to review such drugs on the basis of information submitted by the drug manufacturers. All NDA holders whose approval had been obtained on the basis of safety only were directed to submit to NAS–NRC "the best data available" to support claims made for their drugs. 31 Fed. Reg. 13014. When NAS–NRC completes its evaluation of a drug, it submits a report and recommendation to the Commissioner. On the basis of such reports and any other information indicating a lack of substantial evidence of effectiveness, the Commissioner can initiate procedures under Section 505(e) leading to possible withdrawal of approval. Between October 1967 and April 1969, 2,824 reports were submitted, covering approximately 3,700 drugs manufactured by 237 companies.[2]

It soon became apparent to FDA that it could not effectively deal with the large volume of drugs for which no substantial evidence of effectiveness was available if it proceeded under then-effective regulations, which afforded a full administrative hearing prior to withdrawal to any manufacturer making a timely request for one. Accordingly, on September 19, 1969, FDA published regulations defining the scientific content of studies which would constitute substan-

[2] National Academy of Sciences, Drug Efficacy Study, Final Report to the Commissioner of Food and Drugs, p. 5.

tial evidence within the meaning of Section 505(d), and limiting the right to a hearing to those applicants whose requests were supported by such evidence (34 Fed. Reg. 14596). On the same day, these new regulations were applied to a final order withdrawing approval of certain combination antibiotic drug products. The withdrawal order was affirmed on appeal, *Upjohn Co.* v. *Finch,* 422 F. 2d 944 (C.A. 6), but the agency was enjoined in another proceeding from further action under the regulations, because they had been published without affording interested parties an opportunity for comment. *Pharmaceutical Mfrs. Assn* v. *Finch,* 307 F. Supp. 858 (D. Del.). On May 8, 1970, after consideration of industry comments, the regulations were republished in amended form (35 Fed. Reg. 7250). These regulations (21 C.F.R. 130.12 (a)(5) and 130.14) were thereafter upheld as consistent with the statute and the requirements of due process. *Pharmaceutical Mfrs. Assn* v. *Richardson,* 318 F. Supp. 301 (D. Del.).[3]

2. *Proceedings Below.* In 1953, the Food and Drug Administration approved an NDA filed by Hynson, Westcott and Dunning, Inc., for a prescription drug,

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[3] Prior to the decision below in the instant case, actions taken by the Commissioner under the regulations governing summary withdrawal procedures and under parallel regulations for decertification of antibiotic drugs had been uniformly upheld in the courts of appeals. See *Ciba-Geigy Corp.* v. *Richardson,* 446 F. 2d 466 (C.A. 2); *Pfizer, Inc.* v. *Richardson,* 434 F. 2d 536 (C.A. 2); *Upjohn* v. *Finch, supra*; see also *American Cyanamid Co.* v. *Richardson,* 456 F. 2d 509 (C.A. 1) (opinion by Coffin, J., denying motion to stay order of withdrawal).

Lutrexin,[4] the active ingredient of which is lututrin, which is indicated for use in premature labor, threatened and habitual abortion, and dysmenorrhea. The agency advised the manufacturer that it doubted the drug's effectiveness for its intended uses (JA I, 1),[5] but, under the statute in effect at that time, it was obliged to approve the NDA based upon consideration of the drug's safety only.

Pursuant to the arrangement for review of effectiveness of drugs described above, an NAS–NRC panel evaluated Lutrexin for each of its recommended uses and reported to the Commissioner. Although the panel's stated conclusion was that the drug was "possibly effective," its comments made clear that it found a lack of adequate, controlled studies affording satisfactory evidence of the drug's effectiveness. It recommended that each claim be considered "inappropriate" or "unwarranted" unless documentation were provided (JA I, 7–8). On May 24, 1968, after review of these findings, the Commissioner published a notice inviting Hynson to submit additional evidence of the drug's claimed effectiveness (JA I, 11). On March 22, 1969, having considered additional material submitted but still finding no substantial evidence of effectiveness, the Commissioner published notice of his intention to withdraw approval of the drug and notice to

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[4] The administrative proceedings also involved a companion drug, Trexinest, the marketing of which has since been discontinued.

[5] "JA" refers to the two-volume Joint Appendix in the court of appeals.

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Hynson of its opportunity for a hearing prior to withdrawal (JA I, 13). At that time, the agency's rules still provided for a hearing upon timely request by any adversely affected party, and Hynson so requested (JA I, 16).

The hearing was never commenced, however. Instead, Hynson filed a complaint for declaratory and injunctive relief in the United States District Court for the District of Maryland, claiming to be exempt from the efficacy review provisions of the 1962 Drug Amendments (JA I, 17). On September 11, 1970, the district court dismissed that action, holding that the issues presented were within the primary jurisdiction of FDA and that Hynson had failed to exhaust its administrative remedies (JA I, 26). No appeal was taken from that judgment.

While the case was pending in the district court, FDA adopted its new regulations, discussed above, establishing standards for the submission of "substantial evidence" to furnish a basis for a hearing prior to withdrawal of approval. Parties subject to pending withdrawal proceedings were given additional time to supplement their original hearing requests to bring them into compliance with the new rules (JA I, 21). Hynson declined to amend its request, taking the position that its right to a hearing had already vested under the old rules applicable at the time of its original request (JA I, 23–24).

Following dismissal of its lawsuit, Hynson renewed its request for an administrative hearing (JA I, 27). Although continuing to claim an absolute right to a hearing under the old rules (JA I, 27–28), it also

listed what it contended was substantial evidence of Lutrexin's effectiveness (JA I, 30–35). This listing consisted primarily of material previously submitted to NAS–NRC or to FDA, supplemented by certain affidavits and reports of medical studies which had been submitted to the district court (JA I, 36–37).

On May 31, 1971, the Commissioner issued an order noticing withdrawal of new drug approval for Lutrexin, and, *inter alia,* denying Hynson's request for a hearing (App. C, *infra,* pp. 14a–22a). In denying a hearing, the Commissioner found that Hynson was obliged to comply with the currently applicable regulations (*id.* at 16a) and that it had failed to comply (*id.* at 17a). He pointed out that it had failed to identify what, if anything, in the mass of material submitted, it relied upon as "substantial evidence" of effectiveness. Most of that material had previously been considered by the NAS–NRC panel, and such studies as were included were unaccompanied by any of the documentation required by the new regulations to show that they were adequate and well-controlled. The Commissioner also dealt specifically with those published and unpublished studies cited by Hynson which had not previously been submitted to NAS–NRC or to the agency. He demonstrated how each showed deficiencies on its face that prevented it, under the rules, from being treated as an adequate and well-controlled study (*id.* at 17a–20a).

On appeal, the court of appeals set aside the withdrawal order. It found the "crucial" issue to be the statutory requirement of an opportunity for a hearing (App. A, *infra,* p. 6a). It purported not to question

the Commissioner's right to adopt regulations allowing denial of a hearing where no genuine and substantial issue of fact is presented, and it presumed, without explicitly deciding, that this case is governed by the rules in effect at the time of decision, not the time of Hynson's initial request for a hearing (*id.* at 7a). In holding that the test of whether a hearing must be held is "whether there is any 'genuine and substantial' evidence that supports the position of the applicant," the court apparently ascribed to the Commissioner an insistence that the evidence proffered actually prove effectiveness as a predicate to grant of a hearing (*id.* at 7a–8a). It pointed out that Congress adopted the test of "substantial" evidence as an intentionally milder test than "preponderant" or "conclusive" evidence (*id.* at 8a–9a).

The court held (*id.* at 9a):

> * * * the showing of the appellant was such that, under a reasonable construction of the Commissioner's own regulations, as well as under familiar principles of due process, and the requirements of the Administrative Procedure Act, it was entitled to an impartial hearing before its NDA was withdrawn. * * *

The court relied upon several factors: the "possibly effective" rating given the drug by the NAS–NRC panel; the absence of any record evidence of ineffectiveness; the studies and opinions of medical experts of impressive credentials; and the affidavit of a former FDA medical officer that in his opinion Hynson had submitted adequate and well-controlled clinical investigations (*id.* at 9a–10a). The Commissioner's

efforts to demonstrate that deficiencies in Hynson's evidence made it inadequate under the statutory requirement for "adequate and well-controlled" studies were held to be unavailing. Such questions, the court held, are to be resolved in an adversary hearing (*id.* at 11a).

REASONS FOR GRANTING THE WRIT

1. It was the plain purpose of Congress, in the 1962 amendments to the Federal Food, Drug, and Cosmetic Act of 1938, to afford assurance to the American consumer that all drugs available on the market are both safe and effective for their intended uses. The Senate Committee on the Judiciary was "of the opinion that with [the] changes [it proposed] the legislation will insure the reliability of drugs" (S. Rep. No. 1744, Part II, 87th Cong., 2d Sess., p. 1). To achieve this end, Congress deliberately placed a heavy and precisely defined burden upon the drug manufacturer to prove the effectiveness of a drug it seeks to market by requiring that claims of effectiveness for new drugs be supported by "substantial evidence" (Section 505 (e)). Only evidence of a particular kind was declared to be "substantial," *viz.*: "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved * * *" (Section 505(d)).

That the choice of this exacting standard was purposeful is apparent from a review of the legislative history. An impressive succession of scientific experts testified that the opinion evidence of physicians testi-

fying only from observation and personal experience is an inherently unreliable indicator of drug effectiveness. These witnesses persuaded Congress to insist upon adequate and well-controlled clinical investigations in support of claims of drug efficacy. This legislative history has been exhaustively considered by courts that have upheld the statutory standard and the Commissioner's interpretive rules thereunder. See *Upjohn Co.* v. *Finch*, *supra*, 422 F.2d at 950–954; *Pharmaceutical Mfrs. Assn* v. *Richardson*, *supra*, 318 F. Supp. at 306–309.

The Commissioner's congressionally assigned responsibility to remove ineffective drugs from the market presents an enormous task, involving evaluation of more than 4,000 drug products (and approximately 16,700 separate claimed uses for the products) that had been granted approved NDAs between 1938 and 1962. Evaluation of these products, with the assistance of NAS–NRC, has led to the initial conclusion that approximately 2,800 are effective for at least one claimed use, 200 are "probably effective," 600 are "possibly effective," and 550 are ineffective.[6] Drug products in any category other than "effective" are potentially subject to withdrawal of approval unless their effectiveness can be established in accordance with the statutory standard. FDA has thus been faced with the problem of dealing with 1,350 suspect drug products (not to mention the numerous other

[6] With respect to claims, FDA estimates that approximately 12,500 of the 16,700 claims made for drug products are not in the "effective" category.

instances where a drug in the "effective" category makes claims for uses as to which it may not be effective).

A great many of these products fall in the suspect categories because the data existing to support their claims of effectiveness do not meet the congressional standard of "substantial evidence" of effectiveness, since they are not based on adequate and well-controlled clinical investigations. Accordingly, in order to make manageable the responsibility imposed by Congress to withdraw approval of drugs lacking substantial evidence of effectiveness and still meet its obligation to hold hearings when substantial factual issues exist, FDA adopted the regulations at issue here. These regulations carefully define what constitutes "adequate and well-controlled investigations" (21 C.F.R. 130.12(a)(5)) and require the manufacturer seeking a hearing on effectiveness to submit studies apparently meeting these standards, failing which an order of withdrawal may be entered without a hearing (21 C.F.R. 130.14). The latter provision has been approvingly described as a "threshhold requirement" (*American Cyanamid Co.* v. *Richardson*, 456 F. 2d 509, 513 (C.A. 1)), and as a duty to present "the evidence needed to make out a *prima facie* case" (*Ciba-Geigy Corp.* v. *Richardson*, 446 F. 2d 466, 468 (C.A. 2)); it means no more than that a hearing would be a time-consuming and useless formality unless the manufacturer is prepared to present evidence of the precise type that Congress has required to support a decision in its favor.

The decision of the court of appeals in the instant case, while purporting to accept the validity of FDA's regulations and merely to reject the application of the regulations in this case, in reality rejects the entire purpose and utility of the regulations by imposing a standard that would necessitate a hearing in nearly every case. Hynson here sought to prove effectiveness through evidence the great majority of which consisted of medical opinion based upon experience and observation. However impressive such evidence may appear to laymen, this is precisely the type of proof Congress rejected as a basis for a showing of efficacy. Hynson did offer a few published and unpublished studies, but the NAS–NRC had little difficulty concluding that they did not meet the medical community's standards of adequacy (JA I, 7–8), and the Commissioner specifically identified how each fell short of compliance with the standards of 21 C.F.R. 130.12 (App. C, *infra*, pp. 17a–20a).

If the regulations are valid, therefore, the only issue that was before the court was whether the Commissioner's specific findings that Hynson had failed to meet the criteria for "adequate and well-controlled investigations" constituted a reasonable and adequately supported determination.[7] Instead, the court

[7] A recent decision of the court of appeals for the District of Columbia Circuit, *USV Pharmaceutical Corp.* v. *Secretary of Health, Education, and Welfare*, No. 24,900, decided August 14, 1972, set aside an order withdrawing approval of a drug without a hearing in a case which held that the Commissioner had failed at any stage of the proceeding to "present anything approaching a prima facie showing that there was no genuine and substantial issue of fact requiring a hearing" (slip op.,

found that the issue of effectiveness was raised sufficiently to warrant a hearing by such factors as (1) the absence of expert opinion that Lutrexin is ineffective, (2) the NAS–NRC conclusion that it was "possibly effective," (3) its safety, (4) the opinion of a former FDA employee that the studies of Lutrexin represented " 'well-controlled' clinical studies," and (5) the possibility that, after further inquiry at a hearing, it would turn out that the studies, notwithstanding their facial defects, would qualify under the regulations (App. A, *infra*, pp. 9a–11a).

The first three of these considerations clearly provide no support for the court's decision, since the statute imposes no burden on FDA to prove a drug ineffective and these considerations do not in any way indicate the existence of "substantial evidence" of effectiveness. The conclusions of the former FDA medical officer, while relevant, are immaterial because they fail to indicate any specific alleged error in the carefully detailed conclusions of the Commissioner

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p. 12). In the course of its opinion, the court indicated that, before requiring the manufacturer to submit material in support of a right to a hearing, the Commissioner was obliged to make a *prima facie* showing of facts and reasons leading to the conclusion that there was no genuine issue requiring a hearing. The court analogized the situation to the requirement imposed upon the movant for summary judgment in a civil suit.

This position, in our view, wrongly shifts the burden of producing evidence of effectiveness away from the applicant, where Congress intended it to be. In any event, the Commissioner's withdrawal order here contained a thorough and reasoned evaluation of the materials submitted in support of Hynson's claims of efficacy and correctly held them to be insufficient to raise a material issue of fact.

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regarding the adequacy of the studies.[8] As to the final consideration, it is of course always possible that a hearing would produce new information justifying a different conclusion about a given question, but surely neither the statute nor the regulations require the Commissioner to hold a hearing on the basis of such speculative possibilities. Instead, the statute and regulations are designed to accomplish expeditious removal from the market of drugs that are not of proven effectiveness. And sponsors of such drugs who, like Hynson, have failed to come forward with the kind of proof of effectiveness Congress has required are, of course, free in the future to submit new studies of efficacy in support of another new drug application for the same product.

It is thus apparent that the decision below is antithetical to the statutory policy and, in effect, invalidates the Commissioner's regulations implementing that policy. The evidence on which the court here relied is precisely the type of evidence Congress rejected as unreliable for purposes of the 1962 amendments. It is a type of evidence that very likely can be produced by the manufacturer in virtually every withdrawal proceeding. If the agency is to be compelled to conduct a full evidentiary hearing in every case where this type of proof is offered, it is difficult to see how

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[8] The witness, who was by then an officer of a major drug manufacturer, gave his affidavit in January 1970 (JAI, 76–77). His original views as to what constitutes adequate and well-controlled studies were published in 1964 (JAI, 86–94). The Commissioner's regulations defining the necessary content of such studies were promulgated on May 8, 1970.

or when it will be able to complete its fundamental task under the 1962 amendments of removing from the market drugs of unproved effectiveness.[9]

The basic error of the court below, in our view, was its failure properly to relate the procedural requirements for an evidentiary hearing to the substantive standards for withdrawal. The procedural regulations at issue here are based on the well-established principle that, even under statutes requiring a hearing, Congress did not intend agencies "to waste time on applications that do not state a valid basis for a hearing." *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192, 205; *Federal Power Commission* v. *Texaco Inc.*, 377 U.S. 33, 39. No hearing need be afforded if no material issue of fact is in dispute.[10] Whether such an issue is present can be determined only by reference to the specific substantive standards governing the proceeding. Here, as previously discussed, the 1962 amendments to the Act declare in Section 505(e) that

[9] In marked contrast to the court below, the District Court for the District of Columbia recently ruled that FDA has moved too slowly in discharging its responsibility to review the efficacy of drugs that had been approved for marketing prior to the 1962 amendments. *American Public Health Ass'n* v. *Veneman*, Civ. Action No. 1847–70, decided August 23, 1972. Manifestly, the agency will be unable to satisfy the thrust of that decision to expedite review and appropriate withdrawal actions if it must meet the standard for granting evidentiary hearings prior to withdrawal that has been imposed by the court of appeals in the instant case.

[10] See, *e.g.*, *Municipal Light Boards* v. *Federal Power Commission*, 450 F. 2d 1341, 1345 (C.A.D.C.); *Citizens for Allegan County* v. *Federal Power Commission*, 414 F. 2d 1125, 1128 and n. 5 (C.A.D.C.); *Virginia Electric and Power Co.* v. *Federal Power Commission*, 351 F. 2d 408, 410 (C.A. 4).

approvals shall be withdrawn if there is "a lack of substantial evidence" of effectiveness, and they expressly define substantial evidence in Section 505 (d) to mean "adequate and well-controlled investigations, including clinical investigations, by experts * * * on the basis of which it could * * * be concluded by such experts that the drug will have the effect * * *" claimed for it. The substantive issue pertinent here, therefore, is whether the investigations are adequate to permit experts to conclude that the drug is effective. Accordingly, the procedural issue under the regulations is whether the data proffered by the applicant are sufficient to raise this specific question at all—and not, as the court of appeals would have it, merely whether there is, in a more general sense, a "genuine issue of fact on the effectiveness of Lutrexin" (App. A, *infra*, p. 11a). If it is patent that the studies proffered are not "adequate and well-controlled investigations," no amount of testimony or cross-examination can make up the deficiency. See *Upjohn Co.* v. *Finch, supra,* 422 F. 2d at 955.

2. The decision below is subject to two possible interpretations: (1) that the proffer by the manufacturer of respectable evidence of effectiveness, even if not consisting of "substantial evidence" in the form of "adequate and well-controlled investigations" as required by Section 505(d) and 21 C.F.R. 130.12, is sufficient to raise an issue of effectiveness requiring resolution through an evidentiary hearing; or (2) that even if FDA is justified in conditioning the right to such a hearing upon a showing of "substantial evidence" as defined by statute and regulation, the

threshold determination of whether such a showing has been made itself requires an evidentiary hearing. Under either view, the decision basically conflicts with the rulings in *Pfizer, Inc.* v. *Richardson*, 434 F. 2d 536 (C.A. 2), and *Upjohn Co.* v. *Finch*, 422 F. 2d 944 (C.A. 6). The decision also conflicts with the thorough and carefully reasoned opinion of the district court in *Pharmaceutical Mfrs. Ass'n* v. *Richardson*, 318 F. Supp. 301 (D. Del.), upholding the validity of the regulations at issue here.

In both *Upjohn* and *Pfizer*, the Commissioner had withdrawn approval for certain antibiotics without a hearing.[11] In each instance, the manufacturer had submitted a large quantity of material that it contended demonstrated the effectiveness of the product, both as a general proposition and under standards like those of 21 C.F.R. 130.12. In each instance, the court of appeals upheld the Commissioner's action, concluding that he could properly refuse a hearing, no matter how much other evidence of effectiveness was produced, in the absence of a *prima facie* showing of the existence of "adequate and well-controlled investigations" (434 F. 2d at 544–546; 422 F. 2d at 950–955), and upholding the Commissioner's threshold, non-hearing determination that the manufacturer had failed to show the existence of such investigations (434 F. 2d at 546–547; 422 F. 2d at 951). With respect to the latter question, Judge Friendly observed for the court in *Pfizer* that "such a determination is

[11] The antibiotics involved in *Upjohn* generated revenues of about $30 million annually and represented a substantial portion of the manufacturer's total sales.

peculiarly within the FDA's expertise and we would be reluctant to intrude into medical matters we do not truly understand * * *" (434 F. 2d at 546). In contrast to the court below, the court in *Pfizer* concluded that the specific deficiencies detailed in the Commissioner's order (comparable to those specified in the order here) showed "that the FDA had a reasonable basis for considering that Pfizer's submissions did not comply with the requirement of the statute and the Regulation" (*id.* at 547). This, we submit, is the standard the court in the instant case also should have applied.

The only difference between the instant case and *Pfizer* or *Upjohn* is that the latter involved antibiotics under Section 507 (21 U.S.C. 357) rather than new drugs under Section 505. This difference is immaterial, however, since the basic statutory and regulatory scheme with regard to both types of products involves the same withdrawal of approval for ineffectiveness and the same "substantial evidence" requirement. Indeed, the Second Circuit, in *Ciba-Geigy Corp.* v. *Richardson,* 446 F. 2d 466, subsequently upheld as "reasonable and salutary" (*id.* at 468) the preconditions to evidentiary hearing in new drug cases specified in the regulations at issue here.

The issues presented by the decision below are of great importance to the Food and Drug Administration and the drug industry, and of special importance to the American consumer, for whom Congress sought to assure the reliability and effectiveness of prescription drugs. At the very least, this decision creates

undesirable confusion concerning questions apparently settled by previous decisions of other courts of appeals. If it is permitted to stand, the efforts of the Commissioner of Food and Drugs to implement the efficacy provisions of the 1962 drug amendments with respect to drugs marketed prior to their adoption will be seriously impaired.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

ERWIN N. GRISWOLD,
Solicitor General.
THOMAS E. KAUPER,
Assistant Attorney General.
ANDREW L. FREY,
Assistant to the Solicitor General.
GREGORY B. HOVENDON,
Attorney.

PETER BARTON HUTT,
Assistant General Counsel,
Food, Drugs, and Product Safety Division,
United States Department of Health,
Education, and Welfare.

SEPTEMBER 1972.

APPENDIX A

United States Court of Appeals for the Fourth Circuit

No. 71-1717

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, PETITIONER

v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, RESPONDENTS

On Petition to Review an Order of the Commissioner of Food and Drugs

Argued February 7, 1972. Decided May 24, 1972.

Before BUTZNER, RUSSELL AND FIELD, *Circuit Judges.*

Edward Brown Williams (Jan Edward Williams and Harter, Calhoun and Williams, Robert H. Patterson, Jr., and McGuire, Woods and Battle, and John Kyle Worley on brief) for Petitioner, and Gregory B. Hovendon, Attorney, Department of Justice, (Richard W. McLaren, Assistant Attorney General, and Peter Barton Hutt, Assistant General Counsel, Food, Drugs and Environmental Health Division, Eugene M. Pfeifer, Attorney, United States Department of Health, Education, and Welfare, on brief) for Respondents. Joel E. Hoffman (Robert L. Wald, Selma M. Levine, and Wald, Harkrader and Ross on brief) for Amicus Curiae.

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RUSSELL, *Circuit Judge:*

The appellant, a drug manufacturer, seeks review of a final order withdrawing marketing approval (NDA) of the drug Lutrexin by the Commissioner of Food and Drugs, Department of Health, Education and Welfare.[1] The appellant alleges error in such order of withdrawal (1) for failure to sustain its claim of exemption from withdrawal on account of lack of "substantial evidence" of effectiveness of its drug and, if this claim of exemption is overruled, (2) for denial of a hearing, as required under the applicable statute, on its showing of effectiveness. We reverse.

The appellant was granted an approved NDA for Lutrexin in 1952. At that time, the Food, Drug and Cosmetic Act of 1938 conditioned such grant on general recognition of safety of the drug approved. In 1962 the Act was amended to authorize withdrawal of an approved NDA for any drug for which the Commissioner "after due notice and opportunity for hearing", found there was "a lack of substantial evidence of effectiveness."[2] The term "substantial evidence" was defined in the Amendments as "consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[3] There was an exemption from these requirements for drugs, which, *inter alia,* were not

[1] Section 355(h), 21 U.S.C.
[2] Section 355(e), 21 U.S.C.
[3] Section 355(d), 21 U.S.C.

covered on the day immediately before the enacting date of the Amendments (i.e., October 9, 1962) by an "effective NDA".[4]

In carrying out his new responsibilities under the Amendments, the Commissioner secured the services of the National Academy of Sciences-National Research Council (NAS–NRC) for reviewing the claims of effectiveness on behalf of any drugs NDA'd between 1938 and 1962.[5] To facilitate its assignment, NAS–NRC set up a Drug Efficacy Study Group and all drug manufacturers with approved NDAs obtained between 1938 and 1962 were directed by the Commissioner to submit to this Group evidence "pertinent to the evaluation of the effectiveness of the(ir) drugs."[6] The appellant submitted to the Group clinical data, investigations and studies in support of the effectiveness for its drug Lutrexin. After considering such data, NAS–NRC concluded that Lutrexin was "possibly effective" but indicated the supporting documentation was inadequate.

The Commissioner advised the appellant of his concurrence with the conclusions of NAS–NRC and, as required by the statute, extended to it an opportunity for a hearing on the proposed withdrawal of the ap-

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[4] "In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force * * *, and (C) was not covered by an effective application under section 505 of that Act * * *, the amendments to section 201(p) * * * made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day." Section 107(c)(4), appended to Section 321, 21 U.S.C., 1972 Supplement, p. 192.

[5] 21 F.R. 13014, October 6, 1966.

[6] 21 F.R. 13014.

proved NDA for Lutrexin.[7] At such a hearing, the appellant was advised it might "produce evidence and arguments why approval * * * should not be withdrawn."[8] The appellant in due time requested such hearing. Under the Commissioner's regulations, a hearing was required within 90 days after such request, unless the parties agreed otherwise.[9] However, although no delay was agreed on, hearing within such period was not had. The delay on the part of the Commissioner in setting a hearing was due to litigation over the procedure to be followed by it in implementing its efficacy review and in conducting hearings resulting therefrom.[10] It is unnecessary to review the difficulties encountered in developing valid regulations for such hearings. It is sufficient for the issues here that it was not until May 8, 1970, that the legal objections to the regulations were finally resolved.

During this interregnum when the regulations of the Agency were under challenge and the Commissioner was delaying a hearing, the appellant, whose request for a hearing had been delayed for more than a year, sought in District Court a declaratory judgment to the effect that, under the exemption clause included in the 1962 Amendments, Lutrexin was not a "new drug" on and before October 10, 1962, and was thereby exempt from the requirement of evidence of effectiveness under the Amendments. Such action was dismissed on the ground that primary jurisdiction to resolve the issue of exemption under the Act rested with the Commissioner. No appeal was taken from this dismissal.

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[7] 33 F.R. 7701.

[8] 34 F.R. 5556.

[9] 21 C.F.R. 130.14(b).

[10] See *Pharmaceutical Manufacturers Association* v. *Finch* (D.C.Del. 1970) 307 F. Supp. 858; *Upjohn* v. *Finch* (6th Cir. 1970) 422 F. 2d 944; and *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536.

While this declaratory action was pending, the Commissioner issued his new regulations detailing the circumstances under which an applicant might secure a hearing on a proposal by the Commissioner for withdrawal of an effective NDA. By these regulations, the Commissioner was authorized to deny a hearing, "when it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data".[11]

After the regulation had been legally promulgated, which was more than a year after the appellant had requested a hearing, the Commissioner directed the appellant's attention to these new regulations and suggested that it amend its request for a hearing to comply. Though it contended it had, by its earlier request, perfected its right to a hearing and was not obligated to amend its request, the appellant did, following the dismissal of its declaratory action, submit a considerable amount of clinical medical studies and investigations in support of the claim of effectiveness for its product by way of compliance with the new regulations. The Commissioner, however, dismissed the appellant's request for a hearing on the basis of such showing, finding (1) that its drug was a "new drug" requiring proof of effectiveness, and (2) that its showing of effectiveness was insufficient to demonstrate a "genuine and material issue of fact" under the test of "substantial evidence" as defined in the Amendments.

[11] 21 C.F.R. 130.14(b).

On the basis of these findings it withdrew the approved NDA for Lutrexin. It is from this order that appeal has been taken.

I

The appellant's claim to an exemption for its drug is easily disposed of. We have held in a related case that a drug covered by a pre-1962 approved NDA, which had not been withdrawn under the procedure set forth in Section 505(e), is not entitled to the exemption granted under Section 107(c)(4) of the Amendments.[12] The appellant's NDA was outstanding and had not been legally withdrawn on October 10, 1962. It cannot accordingly claim the benefit of the exemption statute for its drug. While the appellant was entitled to have this issue resolved by the District Court, it was not prejudiced by, and cannot complain of, the refusal by the District Court to exercise jurisdiction. Nor, for that matter, did the appellant appeal and is accordingly without standing in this proceeding to challenge that dismissal.

II

The crucial issue in this case, however, is posed by the appellant's second contention and revolves about the requirement in the Act that, before the entry of a final order of withdrawal, the applicant be given an "opportunity for hearing". At such a hearing, the procedure adopted by the Commissioner allows the applicant to "produce evidence and arguments to show why approvals of (its drugs) * * * should not be withdrawn."[12a] Of course, the Commissioner might, as he

[12] *USV Pharmaceutical Corp.* v. *Richardson*, (4th Cir. 1972) ——— F. 2d ———.

[12a] Whether this is too narrow and improperly confines the scope of the hearing, so far as it is adjudicatory, see Davis, *The Requirement of a Trial-Type Hearing*, 70 Har. L. Rev. 193 (1956).

did by his regulations issued in 1970, provide for the denial of a hearing where it clearly appeared from the applicant's own showing there was no "genuine and substantial issue of fact" on which the claim of the applicant might be sustained. *Ciba-Geigy Corp.* v. *Richardson* (2d Cir. 1971) 446 F. 2d 466, 468. It may be assumed that such regulation, when issued will apply to all pending applications. *U.S.* v. *Storer Broadcasting Co.* (1956) 351 U.S. 192, 205. But, in applying this regulation and in making his determination thereunder, the Commissioner's discretion is not absolute. Neither due process nor the Administrative Practice Act permits an arbitrary denial in any case where it can be fairly said there are "genuine and substantial issues of fact" in dispute.[13]

Such a denial would, in addition, be violative of the Congressional purpose expressed in the provision for a hearing. And the courts must see that such Congressional purpose is not thwarted by administrative usurpation; or, as the Court said in *Environmental Defense Fund, Inc.* v. *Ruckelshaus* (D.C.C.A. 1971) 439 F. 2d 584, 596, the courts have "an obligation to ensure that the administrative standards conform to the legislative purpose * * *." Accordingly, only if

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[13] See *Ciba-Geigy Corp.* v. *Richardson*, *supra*, at p. 468. The question is analogous to that presented by a demand for a hearing in connection with an N.L.R.B. election where the right to a hearing subject to the same general limitations as stated in the Commissioner's regulations, and it would seem the same test of the right to a hearing is applicable. For the rule in such N.L.R.B. case, see *N.L.R.B.* v. *Bata Shoe Co.* (4th Cir. 1967) 377 F. 2d 821, 825–6; *United States Rubber Co.* v. *N.L.R.B.* (5th Cir. 1967) 373 F. 2d 602, 606; *N.L.R.B.* v. *Smith Industries, Inc.* (5th Cir. 1968) 403 F. 2d 889, 892–5.

it can be fairly said that the clinical tests and medical studies and investigations submitted by the applicant, if credited and accepted, will not support a finding that they provide "substantial evidence" of effectiveness was it proper for the Commissioner to deny the appellant a hearing *before* entering a final order of withdrawal. The judicial test is somewhat the converse of that to be applied in a review of a decision of the Commissioner entered *after* a hearing. In that instance, his decision is to be upheld, if sustained by any substantial evidence.[14] But in determining whether the Commissioner acted within the limits of his discretion on the procedural question of whether a hearing is to be allowed, the test is whether there is any "genuine and substantial" evidence that supports the position of the applicant.

Manifestly, the applicant does not have to satisfy or convince the Commissioner by his evidence that his product is effective as a predicate for securing his right to a hearing. If that was his burden, a hearing would never be necessary or appropriate. If he, by his showing, convinced or satisfied the Commissioner, the proposed withdrawal would naturally be denied; on the other hand, if he failed to satisfy, then the Commissioner would deny a hearing and order withdrawal. In either event, a hearing would be useless and the Congressional promise of a hearing would be purely illusory. No such exacting standard of proof is required as a basis simply for the right to be heard; as has been observed, all that is required for securing a right to a hearing is that the showing be such that, if accepted, a finding of "substantial evidence" of effectiveness would be supportable. And "substantial" in this connection does not mean "preponderant evidence" or "conclusive evidence". Congress specifically

[14] Section 355(h), 21 U.S.C.

discarded those terms for the milder term "substantial," which was understood to embrace the idea, not of a preponderance but rather of a responsible body of qualified opinion."

Applying the foregoing principles, we are of opinion the showing of the appellant was such that, under a reasonable construction of the Commissioner's own regulations, as well as under familiar principles of due process, and the requirements of the Administrative Procedure Act, it was entitled to an impartial hearing before its NDA was withdrawn. It must be noted that no qualified expert has given an opinion that Lutrexin is ineffective for the uses in-

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"In the course of committee deliberation a distinction evolved * * * between two tests the "preponderant evidence" test and the "substantial evidence" test as now specifically defined. Under the former a claim would not be accepted under the new drug section unless it represented the preponderant view of experts * * * the committee recognizes that in the difficult area of drug testing and evaluation there will frequently, if not usually, be a difference of responsible opinion. The committee feels the existence of such a difference should not result in disapproval of a claim of effectiveness if it is supported by substantial evidence defined in the manner set forth below [that is adequate and well controlled investigations by qualified experts upon the basis of which conclusions made be fairly and responsibly drawn.].

[Application of the substantial evidence test means that] a claim could be rejected if it were found (a) that the investigations were not "adequate"; (b) that they were not "well-controlled"; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which its application is made; or (d) that the conclusions to be drawn by such experts could not fairly and responsibly be derived from their investigation.

S. Rep. No. 1744, 87th Cong., 2nd Sess. Part II, pp. 5–6, and see, 2 U.S. Code Congress. & Administrative News, 87th Cong., 2d Sess., p. 2892 (1962).

tended. The NAS–NRC review concluded it was "possibly effective". Neither is there any contention that it is unsafe when used for the purposes intended. The real basis for the determination by the Commissioner that the appellant had failed to make a showing of any genuine issue of fact on the effectiveness of its drug was the conclusion that the various scientific articles and tests submitted by the appellant were not "adequate and well-controlled clinical investigations" within the statutory definition of "substantial evidence". In his decision, the Commissioner sought to point out the deficiencies in the investigations submitted by the appellant which justified this conclusion. In so doing, he did not impugn the competency or qualifications of the scientists and medical experts whose investigations were cited by the appellant in support of its claim. Their professional qualifications, as they appear in the record, are impressive. Their investigations and opinions, some of which have been published in recognized professional medical journals, are, however, dismissed by the Commissioner with the statement that, "No adequate and well-controlled clinical investigations published in the medical literature had been identified."

In making that statement, he disregards the categorical opinion of his former Director of the Bureau of Medicine and Medical Director that the clinical tests and investigations submitted by the appellant represented "'well-controlled' clinical studies". He proceeds to fault two investigations published in an authoritative medical journal, submitted by the appellant, because, "There is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced", and "There is no summary or explanation of the statistical methods used in analysis of the data to show that results were not biased or due to chance".

Another unpublished investigation is dismissed because, "Substantiating documentation to establish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided". Two published studies by a clinical professor of Obstetrics at the University of Illinois are criticized, in one instance, because "The report does not state the method of patient selection" and "Concomitant medication is not excluded" and, in the other, because "The method of selection of the patients does not show progressive dilation of the cervix, which is necessary to accurately diagnose premature labor."

Assuming that all the objections by the Commissioner to these clinical studies, conducted as they were by competent medical authorities, may have some validity, they do not justify a final conclusion, made *ex parte,* without a hearing, that it "clearly appears" that there is no genuine issue of fact on the effectiveness of Lutrexin, which is the test under the Commissioner's own regulation for denial of a hearing; at most, they merely create a genuine question of fact to be resolved at a hearing upon proper evidence. Whether the studies were as controlled as they might have been and whether there was a failure in these studies as published to fill in all the details the Commissioner might think appropriate are matters that could be developed at a hearing, after the authors were examined and the reliability of the investigations further inquired into.

The order of the Commissioner, from which this appeal is taken, is set aside for failure to provide the petitioner with an "opportunity for a hearing" before the entry of said order.

Reversed.

APPENDIX B

United States Court of Appeals for the Fourth Circuit

No. 71-1717

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, PETITIONER

v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION, WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, RESPONDENTS

On Petition to Review an Order of the Commissioner of Food and Drugs

THIS CAUSE came on to be heard upon the petition of Hynson, Westcott and Dunning, Incorporated, for review of an order issued against it by Elliot Richardson, Secretary of Health, Education, Welfare, and Charles C. Edwards, Commissioner of Food and Drugs, on May 31, 1971, in proceedings before the said Agency; and upon a certified list in lieu of a transcript of the record; and the said cause was argued by counsel.

ON CONSIDERATION WHEREOF, it is ordered, adjudged and decreed by the United States Court of Appeals for the Fourth Circuit, that the order of the Commissioner, from which this appeal is taken, is set aside for failure to provide the petitioner with an "opportunity for a hearing" before the entry of said order. The order is reversed.

A True Copy, Teste:
Filed May 24, 1972.

SAMUEL W. PHILLIPS,
Clerk.

By J. U. LAYARD,
Deputy Clerk.

APPENDIX C

[Docket No. FDC–D–123; NDA No. 8–986 and 10–144]

HYNSON, WESTCOTT & DUNNING, INC.

Notice of Withdrawal of Approval of New-Drug Applications

On March 22, 1969, there was published in the Federal Register (34 F.R. 5556) a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new-drug applications for drugs containing lututrin on the ground that there is a lack of substantial evidence that lututrin has the effect or contributes to the effect which the drugs purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Hynson, Westcott & Dunning, Inc., Charles and Chase Streets, Baltimore, Md. 21201, holder of NDA No. 8–986, Lutrexin tablets and NDA No. 10–144, Trexinest tablets by the October 16, 1970 letter of its counsel, has requested a hearing on the following issues:

(1) Whether its lututrin drugs are exempt from the efficacy requirements of 21 U.S.C. 355 under section 107(c) of Public Law 87–781; (2) whether its lututrin drugs are "new drugs" within the meaning of 21 U.S.C. 321(p)(1); and (3) whether there is a lack of substantial evidence of effectiveness to support the claims made for Lutrexin.

In support of its request for a hearing on the issue of substantial evidence of effectiveness, Hynson, Westcott, and Dunning, Inc. (hereinafter referred to as "HW&D") has submitted a list of its medical documentation previously filed with the Agency, including all data submitted in connection with NDA No. 10-144, correspondence between HW&D officials and the Agency or other persons, labeling for the lututrin drugs, literature articles submitted to the National Academy of Science-National Research Council, and the HW&D letter of August 18, 1969, in which the company first elected to avail itself of the opportunity for hearing.

To support its hearing request on the contentions that HW&D's lututrin drugs are exempt from the efficacy requirements of 21 U.S.C. 355, the company has submitted copies of its pleadings, legal memorandum, exhibits, and affidavits, as well as the transcript and order in Hynson, Westcott and Dunning, Inc., v. Finch (C.A. No. 21112, D. Md., decided Sept 11, 1970).

The Commissioner of Food and Drugs has reviewed HW&D's request for hearing and the medical documentation submitted, and makes the following findings:

I. *The drugs, their rationale and claims.* a. Lutrexin is labeled as containing 3,000 units of lututrin per tablet. Lututrin is claimed to be a pig uterine relaxing hormone effective in the treatment of functional dysmerorrhea, selected cases of premature labor and threatened and habitual abortion. The package insert claims the drug has demonstrated activity on the living animal uterus, that it relaxes the contracted uterine muscle by direct action thereon, or by blocking pituitary action.

b. Trexinest is labeled as containing 500 units of lututrin and 1.0 milligrams of estrogen, in the form of sodium estrone sulfate, per tablet. Trexinest is recommended for the treatment of menopausal disorders. The package insert claims that the combination is more effective than lututrin or estrogen alone and points to lututrin as the responsible agent in the drug's effectiveness.

II. *The applicable regulations.* HW&D's contention that it has an unconditional right to a hearing is denied. The hearing regulations, 21 CFR 130.14, require that a person seeking a hearing set forth specific facts showing the existence of genuine and substantial fact issues which requires a hearing. The order of May 8, 1970 (35 F.R. 7250) granted persons involved in notices of hearing, including HW&D, 30 days in which to amend their requests for hearing to comply with the new regulations. The company was given actual notice on May 19, 1970, that it was required to comply with these regulations in order to properly avail itself of an opportunity for hearing. Applications of the regulations have been upheld by the courts. Pfizer, Inc. v. Richardson, 434 F. 2d 536 (C.A. 2, 1970); Upjohn Co. v. Finch, 422 F. 2d 944 (C.A. 6, 1970); Pharmaceutical Manufacturers Association v. Richardson, 318 F. Supp. 301 (D. Del., 1970). HW&D is bound by the judgment in the last case cited.

III. *The Request for a Hearing*—a. *The issues of exemption under section 107(c) of Public Law 87-781 and under 21 U.S.C. 321 (p)(1).* The request for a hearing on these issues is denied. The new-drug applications involved had not been withdrawn prior to enactment of Public Law 87-781. They were "deemed approved" under the 1962 amendments to the Act and are subject to withdrawal on the basis of the effectiveness requirements of the amendments.

b. *Lutrexin and Trexinest are new drugs within the meaning of 21 U.S.C. 321 (p)(1).* The conclusions of HW&D's affiants that these drugs are not new drugs cannot be accepted. No adequate and well-controlled clinical investigations published in the medical literature have been identified. Therefore, there is no data base upon which experts can fairly and responsibly conclude that the safety and effectiveness of the drugs has been proven and is so well established that the drugs can be generally recognized among such experts as safe and effective for their intended uses.

The affiants identify 11 studies as establishing the claims made for the drugs. None purports to be an adequate and well-controlled clinical investigation. They may be summarized as follows:

(1) Majewski and Jennings: Uterine Relaxing Factor for Premature Labor, Ob. & Gyn. 5:649–652 (May 1955); and Further Experiences with a Uterine Relaxing Hormone in Premature Labor, Ob. & Gyn. 9:322–325 (March 1957) by the same authors are one study. The first paper is a preliminary study on 20 patients and the latter is the report on enlarged group of 88 patients. The authors acknowledge that results in the total group are less favorable than in the preliminary study, but conclude that the results are encouraging. Concomitant medication was given an unstated number of patients. There is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced. Nine patients out of 88 in whom the drug proved ineffective were excluded from the report for "statistical reasons". Six patients received the drug for less than 3 hours, which the authors without explanation considered too short a time for a true test of effectiveness. There is no summary or explanation of the statistical methods used in analysis of the data to show that results were not biased or due to chance.

(2) Majewski: Statistical Evaluation in The Reduction of the Incidence of Prematurity (1968) is unpublished. The author claims successful treatment in 86 percent of cases treated in his practice over a 10-year period. Substantiating documentation to establish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided. The author acknowledges that some patients with medical complications such as placenta praevia were included in the study. Lutrexin is not claimed to have value in the medical or obstetrical complications of pregnancy which occur in a significant percentage of premature births.

The paring of live birth percentages by number of pregnancies before and after Lutrexin treatment such as in Table I are all inappropriate. For example, of the 24 cases with one previous pregnancy, 11 live births before treatment and 18 live births after treatment are compared. However, for each of the 18 live births after treatment, an additional pregnancy had elapsed so that the number of previous pregnancies associated with the number 18 is two, not one; as such, the number 18 should be compared with the number 16, the total live births for two previous pregnancies.

The data in Table I does not admit of statistical evaluation by the chi-square test since the test is based on the assumption that each number in the columns of Table I is the sum of independent yes or no responses, e.g., for the one patient with seven previous pregnancies, four live births are correlated, thus ignoring the sample size of one and using an erroneous sample size of four.

(3) Rezek: The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luterum in the Treatment of Dysmenorrhea, Am. J. Ob. & Gyn. 66:396-402 (August 1953). The report does not state the method

of patient selection, nor does it indicate comparability of pertinent variables such as severity or duration of diseases. Concomitant medication is not excluded. No explanations of the methods of observation, the recording of results, and steps taken to minimize patient and investigator bias are provided. The historical controls employed are inappropriate.

(4) Rezek: Lutrexin in the Treatment of Premature Labor, Ann. N.Y. Acad. Sci. 75:995–997 (January 1959). The method if selection of the patients does not show progressive dilation of the cervix, which is necessary to accurately diagnose premature labor. The methods of observation and the recording of results are not explained. No statistical evaluation was presented to show that results claimed are significant in terms of the patient population.

(5) Gratton: The Treatment of Infertility and Prematurity Pregnancy Problems (1968) is unpublished. Patients received numerous concomitant therapies until the fifth month of pregnancy which prevents scientific attribution of results of lututrin therapy. The method of patient selection is unexplained.

Statistically the study lacks adequate design and evaluation. There is no showing that the cases studied are representative of the population to which inferences are made. The pairings of live births percentages in Table II cannot be compared since the number of previous pregnancies differs between the pair percentages and there is no data on possible etiologic factors of previous abortions and premature labor.

(6) Gray: Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases (undated) is an unpublished report on 15 selected cases the author has treated. No plan or protocol is provided to allow deter-

mination of the objectives of the study, the method of patient selection, diagnostic criteria of the condition to be treated, laboratory tests to be made, the methods of observation and recording of results. The author's review of his records does not constitute an adequate and well-controlled investigation.

(7) Four papers by Dr. Trythall were listed in the attachment to his affidavit. In only one article is Lutrexin ever mentioned. The three sentences devoted to the drug provide no information whatsoever except that the author claims to have found it effective in his practice.

The affiants state that double blind investigations of lututrin are unethical because the drug is effective and complications of pregnancy may be life-threatening. The Commissioner does not reach that issue, since none of the historically controlled studies relied upon were adequate and well-controlled investigations.

There are other reasons why HW&D's medical data lack merit, but in view of the above finding their delineation is unnecessary.

c. *The issue of substantial evidence of effectiveness.* The request for a hearing on this ground is denied. The regulations, 21 CFR 130.14, require HW&D to submit a well organized and full factual analysis of the clinical and other investigational data it is prepared to prove at a hearing. The request must set forth specific facts showing that there is a genuine and substantial issue of fact requiring a hearing. HW&D has not attempted compliance with these requirements.

Rather than identify and discuss the efficacy data relied upon to support the claims made for its drugs, the company has merely provided a list, extending to four pages, of practically all materials ever submitted to the Agency and the NAS–NRC. The materials are described, for the most part, in general terms (e.g.,

"data submitted in connection with New Drug Application for Lutrexin tablets * * *, Lutrexin bibliography * * *, Trexinest bibliography * * *, reprints and abstracts * * *). What the Commissioner is required to do is determine from this material, what HW&D may or may not consider relevant and, therefore, relies upon. In the case bibliographies, the Commissioner would be required to research each article and then determine if it is relevant, or whether HW&D might consider it relevant. Because such a procedure is not contemplated by the regulation, the request for hearing is denied for failure to comply with applicable regulations.

Apart from the refusal of HW&D to comply with 21 CFR 130.14, the most basic material in the Lutrexin new-drug application reveals a lack of adequate and well-controlled investigations showing that lututrin will have the effect HW&D claims for it.

The only evidence submitted that lututrin may have biological activity in humans when taken orally is a test on nine women by Jones and Smith in which positive results were reported to have been obtained in six subjects. No plan or protocol was stated. No data on the participating patients was provided. No explanation of procedures for patient selection, or criteria for inclusion in the study, or appropriate laboratory tests before and after administration of lututrin was provided. No statistical analysis showing the test population was of significant size or that results obtained were significant is shown. Moreover, there is no evidence that results claimed have ever been reproduced in humans by other investigators.

Therefore, the Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1053, as amended; 21 U.S.C. 355(e)), and under the authority

delegated to him (21 CFR 2.120), finds that on the basis of new information before him with respect to each of said drugs, evaluated together with the evidence available to him when each application was approved, there is a lack of substantial evidence that each of the drugs will have the effects it is purported or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof.

Pursuant to the foregoing findings, approvals of the above new-drug applications, and all amendments and supplements thereto, are withdrawn effective on the date of the signature of this document.

Dated: May 31, 1971.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[F.R. Doc. 71-8557 Filed 6-17-71; 8:46 a.m.]

APPENDIX D

21 C.F.R. 130.12(a)(5) as amended, 35 F.R. 7251, May 8, 1970, provides:

> (a) If the Commissioner determines upon the basis of the application, or upon the basis of other information before him with respect to the new drug, that * * *
>
> (5)(i) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.
>
> (ii) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is "substantial evidence" to support the claims of effectiveness for "new drugs" and antibiotic drugs.
>
> (*a*) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:
>
> (1) A clear statement of the objectives of the study.

(2) A method of selection of the subjects that—

(*i*) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired.

(*ii*) Assigns the subjects to test groups in such a way as to minimize bias.

(*iii*) Assures comparability in test and control groups of pertinent variables, such as age, sex, severity, or duration of disease, and use of drugs other than the test drug.

(3) Explains the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subjective response, and steps taken to minimize bias on the part of the subject and observer.

(4) Provides a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. Level and methods of "blinding," if used, are to be documented. Generally, four types of comparison are recognized:

(i) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients.

(ii) Placebo control: Comparison of the results of use of the new drug entity with an inactive preparation designed to resemble the test drug as far as possible.

(*iii*) Active treatment control: An effective regimen of therapy may be used for comparison, e.g., where the condition treated is such that no treatment or administration of a placebo would be contrary to the interest of the patient.

(*iv*) Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen (therapeutic, diagnostic, prophylactic) the effectiveness of which is established.

(5) A summary of the methods of analysis, and an evaluation of data derived from the study, including any appropriate statistical methods.

Provided, however, That any of the above criteria may be waived in whole or in part, either prior to the investigation or in the evaluation of a completed study, by the Director of the Bureau of Drugs with respect to a specific clinical investigation; a petition for such a waiver may be filed by any person who would be adversely affected by the application of the criteria to a particular clinical investigation; the petition should show that some or all of the criteria are not reasonably applicable to the investigation and that alternative procedures can be, or have been, followed, the results of which will or have yielded data that can and should be accepted as substantial evidence of the drug's effectiveness. A petition for a waiver

shall set forth clearly and concisely the specific provision or provisions in the criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been, employed, what results have been obtained, and the basis on which it can be, or has been, concluded that the clinical investigation will or has yielded substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(*b*) For such an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(*c*) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

(6) Based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; the Commissioner shall within 180 days after the filing of the application inform the applicant in writing of his intention to issue a notice of hearing on a proposal to refuse to approve the application.

(b) Unless by the 30th day following the date of issuance of the letter informing the appli-

cant of the intention to issue a notice of hearing, the applicant:

(1) Withdraws the application; or

(2) Waives the opportunity for a hearing; or

(3) Agrees with the Commissioner on an additional period to precede issuance of such notice of hearing,

the Commissioner shall expeditiously notify the applicant of an opportunity for a hearing on the question of whether such application is approvable as provided in § 130.14.

21 C.F.R. 130.14, as amended, 35 F.R. 7252, May 6, 1970, provides:

(a) The notice to the applicant of opportunity for a hearing on a proposal by the Commissioner to refuse to approve an application or to withdraw the approval of an application will specify the grounds upon which he proposes to issue an order. On request of the applicant, the Commissioner will explain the reasons for his action. The notice of hearing will be published in the Federal Register and will specify that the applicant has 30 days after issuance of the notice within which he is required to file a written appearance electing whether:

(1) To avail himself of the opportunity for a hearing at the place specified in the notice of hearing; or

(2) Not to avail himself of the opportunity for a hearing.

(b) If the applicant elects to avail himself of the opportunity for a hearing, he is required to file a written appearance requesting the hearing within 30 days after the publication of the notice and giving the reason why the application should not be refused or should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition to the notice of opportunity

for a hearing. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data. If a hearing is requested and is justified by the applicant's response to the notice of hearing, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence, not more than 90 days after the expiration of such 30 days unless the hearing examiner and the applicant otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval.

(c) The hearing will be open to the public: *Provided, however,* That if the Commissioner finds that portions of the application which serve as a basis for the hearing contain information concerning a method or process which as a trade secret is entitled to protection, the part of the hearing that involves such portions will not be public unless the respondent so specifies in his appearance.

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-414

HYMAN, WEITZOFF & DUBBINS, INCORPORATED,
Cross-petitioner,
v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS,
Respondents.

CROSS-PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

EDWARD BROWN WILLIAMS
Counsel for Cross-Petitioner
423 Washington Building
Washington, D.C. 20005

Of Counsel:

IAN EDWARD WILLIAMS
HARTER, CALHOUN & WILLIAMS
423 Washington Building
Washington, D.C. 20005

JOHN KYLE WORTHY
26600 Telegraph Road
Southfield, Michigan 48076

Wilson - Epes Printing Co., Inc. - 783-7400 - Washington, D. C. 20001

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Respondents.

CROSS-PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

Cross-Petitioner, Hynson, Westcott & Dunning, Incorporated, respectfully prays that a writ of certiorari issue to review in part the judgment and opinion of the United States Court of Appeals for the Fourth Circuit entered in this proceeding on May 24, 1972.

OPINIONS BELOW

The opinion of the Court of Appeals and its opinion in two related cases, none of which has yet been officially reported, appear in Appendices A, B, and C, *infra*. The Order of the Commissioner of Food and Drugs also appears in Appendix A.[1]

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[1] The Appendices are cited hereafter as "App." They are to be distinguished from Volumes I & II of the Joint Appendix filed below ("Jt. App. I & II").

JURISDICTION

The judgment of the United States Court of Appeals for the Fourth Circuit was entered May 24, 1972. The jurisdiction of this Court is invoked under 28 U.S.C. Section 1254(1).

EXTENSION OF TIME

By order of August 17, 1972, Mr. Justice Rehnquist extended the time within which to file a petition for a writ of certiorari in this matter (No. A-205) to and including September 11, 1972.

STATUTES INVOLVED

The pertinent statutory provisions, which are set forth in Appendix A, *infra*, are (1) the following sections of the Federal Food, Drug and Cosmetic Act, 52 Stat. 1040, as amended, 21 U.S.C. 301, et seq: Sections 201 (p), 21 U.S.C. 321(p), 502(a), 21 U.S.C. 352(a) and 505, 21 U.S.C. 355, and (2) Section 107 of the Drug Amendments of 1962, P.L. 87-781.

QUESTIONS PRESENTED

The Federal Food, Drug and Cosmetic Act requires manufacturers of "new drugs" as therein defined (Section 201(p)) to obtain pre-marketing approvals of new drug applications for such drugs.

The Act, as amended by the Drug Amendments of 1962, provides for administrative withdrawal-of-approval of a new drug application on the ground that there is a lack of substantial evidence of effectiveness of the subject drug (Section 505(e)(3)). Only drugs "deemed approved" under the amendments (Section 107 (c)(2)) are subject to such administrative withdrawal proceedings. The 1962 Amendments also exempt cer-

tain drugs from all effectiveness provisions and hence from their enforcement either administratively or judicially (Section 107(c)(4) of the amendments). The Food and Drug Administration decided, without a hearing, that cross-petitioner's drug, Lutrexin, is a "new drug," that there is a lack of substantial evidence of its effectiveness, that it was "deemed approved", and that it was not exempt under Section 107(c)(4) of the 1962 amendments.

The Questions presented are:

(1) Whether, in a proceeding to withdraw approval of a new drug application, the Commissioner of Food and Drugs is without authority to determine initially his own jurisdiction to conduct such a proceeding.

(2) Whether one whose drug is subjected to such a withdrawal proceeding is entitled to an administrative hearing at which evidence may be introduced as a basis for deciding whether the Commissioner has jurisdiction to conduct such a proceeding.

(3) Whether a new drug application for a drug which had become generally recognized as safe the day before the effective date of the Drug Amendments of 1962 (October 9, 1962) was no longer an "effective" application within the meaning of Section 107(c)(2) of such amendments and therefore such application was not "deemed approved" under that section.

(4) Whether a drug which had become generally recognized as safe on the day before the effective date of the Drug Amendments of 1962 was a "new drug" on that date and was "covered by an effective application" within the meaning of Section 107(c)(4)(B) and (C) of such Amendments.

STATEMENT

Cross-petitioner, Hynson, Westcott & Dunning, Incorporated (HW&D), sought review in the Court of Appeals for the Fourth Circuit, of an order of the Commissioner of Food and Drugs, published in the Federal Register of June 18, 1971 (36 F.R. 11763, App. B(1), 10a), withdrawing approval of the new drug application (NDA) for HW&D's drugs, Lutrexin and Trexinest.[2] Direct appeal to the Court of Appeals is authorized by Section 505(h), 21 U.S.C. 355(h), of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 301 et seq., the "Act").[3] Under the Act, a "new drug", as therein defined (Section 201(p), 21 U.S.C. 321(p)), cannot be marketed without an approved new drug application.[4]

The Court of Appeals set aside the order of the Commissioner on the ground that HW&D was entitled to a hearing, which had been denied by the Commissioner, on the question of whether approval of HW&D's NDA should be withdrawn under Section 505(e)(3) of the Act, 21 U.S.C. 355(e)(3), as amended in 1962, because there is a lack of substantial evidence of effectiveness of Lutrexin. This cross-petition is filed because, as hereinafter set forth in more detail, the Court (a) decided erroneously that, at the required hearing the Food and Drug Administration (FDA) was without authority to determine its own jurisdiction, (b) decided erroneously one jurisdictional question before it—whether Lutrexin was exempt from the effectiveness requirements of the

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[2] The marketing of Trexinest has been discontinued by HW&D. This case is not concerned with that drug.

[3] Section 505(h) is set forth in Appendix A at 6a.

[4] Marketing of a new drug without an NDA is prohibited by Section 301(d) and 505(a) of the Act, 21 U.S.C. 331(d) and 355(a), under sanction of injunctive, criminal proceedings, or seizure (Sections 302, 303, and 304, 21 U.S.C. 332, 333, and 334).

Drug Amendments of 1962[5] by Section 107(c)(4) of those amendments, (c) failed to deal with the jurisdictional question of whether Lutrexin was exempt from withdrawal-of-approval proceedings under Section 505 (e)(3) of the Act by Section 107(c)(2) of the amendments, and (d) failed to deal with the matter of HW&D's right to a hearing on the two jurisdictional questions above stated and the additional one of whether Lutrexin is now generally recognized as both safe and effective, and, therefore, not a new drug subject to the new-drug provisions of the Act.

HW&D has since 1953 marketed Lutrexin, a prescription drug, for use in the treatment of premature labor, second and third trimester threatened abortion, and dysmenorrhea (menstrual discomfort). The drug was, when first marketed in 1953, a "new drug" within the meaning of Section 201(p) of the Federal Food, Drug and Cosmetic Act as then written. Pre-marketing clearance of Lutrexin under the new drug provisions of Section 505 of the Act was, therefore, necessary, and a new drug application for the drug was filed and became effective on December 23, 1953.

Until 1962 the test under Section 201(p) for determining the necessity for obtaining pre-marketing clearance of a drug was whether the product was generally recognized as safe by qualified experts. Congress, in the Drug Amendments of 1962, amended Sections 201(p) and 505 of the Act to require pre-market clearance of new drugs for both safety and effectiveness. Thus, Section 201(p), as amended, defined "new drugs" as those not generally recognized by qualified experts as both safe *and* effective for their intended uses.

Congress also added to Section 505(d) and (e) the concept of "substantial evidence of effectiveness," a con-

[5] P.L. 87-781.

cept separate and apart from the concept of general recognition of safety and effectiveness. The latter is solely a jurisdictional test. The manufacturer of a product which was a new drug because of a lack of general recognition of effectiveness would, under amended Section 505, in order to obtain approval of an NDA for his product, have to supply FDA with substantial evidence of the effectiveness of the drug. Likewise, where appropriate, FDA could, under Section 505(e)(3), withdraw approval of a new drug's NDA if it found a lack of substantial evidence of the drug's effectiveness.

The Court of Appeals held that HW&D was entitled to a hearing on the question of whether there is a lack of substantial evidence of the effectiveness of Lutrexin. In addition to this point, three basic jurisdictional questions were before the Court of Appeals and argued in HW&D's brief: (1) whether the Commissioner of Food and Drugs was correct in his determination that Lutrexin was not exempt from both *administrative* and *judicial* enforcement of the effectiveness provisions of the Drug Amendments of 1962, by virtue of Section 107(c)(4) of those amendments; (2) whether the Commissioner was correct in his determination that Lutrexin was not exempt by virtue of Section 107(c)(2) of the 1962 Amendments, from *administrative* withdrawal of approval of its NDA under Section 505(e)(3) of the Act on the ground of lack of substantial evidence of effectiveness, and (3) whether in any event the Commissioner was correct in determining that HW&D's product is a new drug subject to the provisions of Section 505 of the Act as amended by the 1962 Amendments. A hearing was denied on these questions.

The Court of Appeals decided the first jurisdictional question adversely to HW&D, following its decision in *USV Pharmaceutical Corporation* v. *Richardson* (4th Cir. No. 71-1596, May 24, 1972, App. C, 45a). It did not

even mention the second and third questions. On May 23, 1972, the day before its decision in the instant case, the Fourth Circuit had held that neither FDA nor the Court of Appeals on direct appeal under Section 505(h), 21 U.S.C. 355(h), had authority to determine the agency's jurisdiction. (*Bentex Pharmaceuticals, Inc.* v. *Richardson*, No. 71-1243, App. C, 29a). Implicit in the Court's decision in HW&D, because of its ruling in *Bentex*, is a holding that FDA did not have the authority to decide these jurisdictional questions.

It is apparent that factual questions underlie the matter of whether Sections 107(c)(2) and (4), or either of them, is applicable to Lutrexin, *viz.*, whether the drug was generally recognized as safe on the day before the effective date of the Drug Amendments of 1962 (October 9, 1962), within the meaning of Section 107(c)(2) and Clause (B) of Section 107(c)(4) of those amendments and was therefore not a new drug on that date; and whether the drug was being marketed in the United States on October 9, 1962 and the labeled conditions of use are now the same as on that date, within the meaning of Section 107(c)(4). Underlying the third jurisdictional question above stated is the factual matter of whether Lutrexin is generally recognized *now* as both safe *and* effective within the meaning of Section 201(p) as amended in 1962. These are adjudicative facts determinative of the jurisdictional questions involved (See affidavits of experts, Jt. App. I, 38 et seq.; medical literature, Jt. App. II).[6]

Because of the *Bentex* ruling, evidence on the factual questions above-stated would not be considered by FDA or introduced at the hearing to which the Court of Appeals said HW&D was entitled since the hearing would

[6] The reference to Jt. App. I and II is to the two volumes filed in the Court below and certified to this Court, and not to the Appendices to this petition.

be limited to the question of whether there is a lack of substantial evidence of the effectiveness of Lutrexin. Yet, if any one of the jurisdictional questions were decided in favor of HW&D, the question of whether HW&D is entitled to a hearing on the Commissioner's proposal to withdraw the license for its product under the new drug provisions of the Act would be moot.

REASONS FOR GRANTING THE WRIT

(1) Introduction

FDA's order withdrawing approval of the NDA for Lutrexin was based on the opinion of a panel of the National Academy of Sciences—National Research Council (NAS-NRC) that the drug was "possibly effective" for the conditions for which it is used.[7]

Lutrexin is one of more than three thousand drugs which were evaluated by panels of NAS-NRC.[8] FDA is still in the process of reviewing the reports of some panels. The status of an unknown but certainly a substantial number of these drugs which were evaluated as "possibly effective" or "probably effective", rather than "effective", will be determined by the interpretations given to the provisions of the Drug Amendments of 1962 here involved. For the reasons stated herein, we believe the Court of Appeals erred in its decision as to the application of Section 107(c)(4) of the 1962 amendments and in its failure to consider the effect of Section 107(c)(2).

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[7] FDA had contracted with NAS-NRC to review the effectiveness of drugs cleared for marketing as "new drugs" between 1938 and 1962 on the basis of proof of safety only.

[8] The Court of Appeals for the District of Columbia recently characterized certain NAS-NRC reports as "cryptic and conclusory, without any statement of supporting facts". *USV Pharmaceutical Corporation* v. *Secretary of Health, Education & Welfare* (No. 24,900, August 14, 1972). The scanty report on Lutrexin may also be so described (See Jt. App. 5).

This case also concerns the fundamental question of whether an administrative agency has the authority to determine its own jurisdiction, subject to statutory review by the Court of Appeals, before acting upon matters before it. The Court of Appeals' decision on this point in *Bentex, supra*, which was followed in the instant case, is in direct conflict with the decision of the Court of Appeals for the Third Circuit in *Ciba Corporation* v. *Richardson*, 3rd Cir., Civil No. 71-1512, (June 5, 1972, App. D, 55a).

Moreover, we submit that in any event this cross-petition should be granted for the reason stated by this Court in granting the Government's petition in *United States* v. *An Article Of Drug, Etc.*, 394 U.S. 784, 791 (1969), *viz.*, that the interpretation involved raise issues of importance in the administration of the Federal Food, Drug and Cosmetic Act.

(2) The Authority Of FDA To Determine Initially Its Own Jurisdiction

The Court of Appeals ruled in *Bentex*, and followed that ruling in the instant case, that only a District Court in an enforcement action brought by the Government or in a declaratory judgment suit brought against the Government, has authority to determine whether and to what extent a drug is subject to the jurisdiction of FDA as a "new drug", that is, whether it is generally recognized as safe and effective and thus is not a new drug or whether it was exempt from the effectiveness provisions of the Drug Amendments of 1962 by Section 107 (c) (2) or 107 (c) (4) of those amendments. The District Court in *Bentex* had held that FDA had concurrent jurisdiction with that court to make such determinations, *O'Neal, Jones & Feldman, Inc.* v. *Richardson*, (D.S.C., Civil No. 70-1001, February 10, 1971). We agree with the District Court.

We have noted that the decision of the Court of Appeals that FDA has no authority to determine its own jurisdiction and that the Court of Appeals may not review such a determination, is in direct conflict with *Ciba Corporation* v. *Richardson*, (3rd Cir., Civil No. 71-1512, June 5, 1972). That Court said:

> "Inherent in the grant of administrative competency to conduct and decide new drug proceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such a proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision" (App. D, 55a, 56a).

The question here involved is of obvious concern to all persons who file NDAs or whose NDAs are the subject of withdrawal proceedings, as is the NDA for Lutrexin. It presents a basic issue of administrative competence to deal with matters whose resolution is essential to a proper disposition of new drug proceedings.

It would not make sense for FDA to withdraw approval of an application for Lutrexin, or any other drug, and for the Court of Appeals to review the order of withdrawal, without a decision upon the issue of whether the subject drug is "new" and therefore within FDA's jurisdiction. One subject to such a proceeding should not be *required* to commence another proceeding in the District Court to obtain initial adjudication of the agency's competence to conduct the administrative proceeding.

The Court of Appeals stated in *Bentex* that "The very filing of the [new drug] application is a concession and recognition by the applicant-manufacturer that the article is a 'new drug'; otherwise there would be no reason to file the application" (App. C(1), 29a, 42a).

This statement reveals a lack of understanding of the realities of the regulatory and public relations problems

of the drug industry. If FDA expresses the opinion that a drug is "new", manufacturers have frequently filed NDAs to avoid enforcement proceedings by FDA, despite their belief that the drug is in fact not a new drug. Litigation with FDA is not welcomed by industry and may cause unfavorable public reaction. The filing of an application may or may not, therefore, indicate a belief that the article is "new".

None of the cases cited by the Court of Appeals in *Bentex* was concerned with the issue of whether an agency has, initially, the authority to determine its own jurisdiction. Moreover, the fact that the jurisdictional question may be decided in enforcement and declaratory judgment actions does not preclude its determination by FDA in administrative proceedings. Evidence upon the question of general recognition can be taken at an administrative hearing as well as in a district court.

FDA and other agencies must constantly decide, initially, whether a particular product or subject matter is within their jurisdiction. It seems apparent to us that otherwise they could not function. The agency itself is in no position to ask a court to decide whether a drug is "new" when a new drug application is filed with it. It must decide the question itself, and has always done so, although it has not designated it as an issue at a hearing. If, on the other hand, the manufacturer of the drug is threatened with adverse action by FDA he should, we think it clear, be able to obtain a decision on the jurisdictional question in the District Court or, on appeal from an Agency determination, in the Court of Appeals.

We can see no reason to doubt that an agency must, where its jurisdiction is at issue, determine that issue before proceeding to decide the merits of other questions before it. It is so held by the courts, *Endicott Johnson Corporation* v. *Perkins*, 317 U.S. 501 (1943) (coverage of Walsh-Healy Public Contracts Act); *Oklahoma Press*

Pub. Co. v. *Walling*, 327 U.S. 186 (1946) (coverage of Fair Labor Standards Act).

We find nothing in the cases which supports the argument that FDA does not have the *authority* to determine, initially, its own jurisdiction. The fact that FDA had refused to make a formal determination on the question prior to the decision in *Hynson, Westcott & Dunning, Incorporated* v. *Finch* (D. Md., Civil No. 21112, decided September 16, 1970)[9] does not militate against this conclusion. It merely indicates that, prior to its change of policy on the matter, there was no adequate administrative remedy on the jurisdictional issue.

Orders of the National Labor Relations Board may be challenged, on jurisdictional grounds, either collaterally (*Leedom* v. *Kyne*, 358 U.S. 184, 188 (1958)), or in the Court of Appeals in an enforcement proceeding (*National Labor Relations Board* v. *Pappas & Co.*, 203 F.2d 569, 571 (9th Cir. 1953)). This, we submit, is the situation under § 505(h) of the Federal Food, Drug and Cosmetic Act. It seems clear to us that the Court of Appeals should, in reviewing an order withdrawing approval of a "new drug" application under that section, determine whether the article is a "new drug," if there is any doubt of its status. Such an order would be of no force or effect if the article were not a "new drug." The threshhold question in this case must be whether FDA correctly concluded that it had jurisdiction over Lutrexin as a "new drug." The question of the validity of the withdrawal of NDA approval for lack of substantial evidence of effectiveness would be moot if the threshhold question were decided in favor of petitioner.

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[9] This was a declaratory judgment suit seeking a declaration that Lutrexin was not subject to the jurisdiction of FDA under the withdrawal of approval provision of Section 505(e)(3). It was dismissed on the ground that FDA had primary jurisdiction. The dismissal was not appealed.

(3) Right To A Hearing On The Jurisdictional Questions

Section 505(e) and the decision of the Fourth Circuit, require that HW&D be afforded a hearing on the question of whether there is a lack of substantial evidence of effectiveness of Lutrexin before withdrawal of approval of the NDA.

It is our position, and the Court in *Ciba Corporation* v. *Richardson*, supra, held, that the authority to determine its own jurisdiction is inherent in the grant of authority to the agency to conduct new drug proceedings. The required hearing is such a proceeding and it appears to us that, where issues of jurisdiction have been raised, as here, the holder of the NDA is entitled to present evidence upon such issues. That is the only logical conclusion where the agency proposes to act under Section 505(e)(3).

Moreover, under the due process clause of the Constitution, we submit that the agency may not make adjudicative determinations (as distinguished from rule-making) without affording adversely affected parties a hearing.[10] The jurisdictional points raised by HW&D before FDA and the Court of Appeals involve substantial questions of adjudicative facts, *e.g.*, whether in any event Lutrexin is now generally recognized as safe and effective for its intended uses.

In the case at bar, FDA held Lutrexin to be a new drug and subject to the effectiveness provisions of the 1962 amendments, and rejected HW&D's request for a hearing on the underlying factual issues. HW&D had submitted to the agency affidavits and other data showing that it had a factual basis for its request for a hearing on these crucial issues. The denial of a hearing cannot, therefore, be justified on the ground that only legal ques-

[10] Davis, Administrative Law Treatise, 1970. Supplement, Sections 7.01, 7.04 and cases there cited.

tions were before the agency. The point was not even mentioned by the Court of Appeals, presumably because it was following its holding in the *Bentex* case that neither FDA in an NDA withdrawal proceeding pursuant to Section 505 of the Act, nor the reviewing court, has the authority to decide jurisdictional questions.

The Court of Appeals emphasized that under principles of due process and the requirements of the Administrative Procedure Act, HW&D was entitled to a hearing before approval of the NDA for Lutrexin could be withdrawn. Surely before, or at least in the course of, conducting a hearing pursuant to the new drug provisions of the Act, due process dictates a hearing on the question of whether Lutrexin is a new drug and subject to withdrawal of approval proceedings under Section 505(e)(3).

(4) Section 107(c)(4) Of The 1962 Amendments

Section 107(c)(4) of the 1962 Amendments specifically made the effectiveness requirements of the amendments inapplicable to drugs which on or before October 9, 1962, (A) were being marketed in the United States, (B) were not "new drugs" and (C) were not then "covered by an effective [new drug] application," if the labeled conditions of use were the same as on that date.

The Court of Appeals held that Lutrexin was not exempt under Section 107(c)(4) of the 1962 Amendments because approval of its NDA had not been withdrawn by FDA under Section 505(e). This construction distorts the purpose and effect of Section 505(e) and makes Section 107(c)(4) meaningless except as applied to so-called "me-too" drugs.[11]

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[11] These are copies of drugs which were once the subject of NDAs but then became "old drugs" thus opening the way for the copies to be marketed without NDAs. There are many such copies.

The *purpose* of Section 505(e) is to prevent the further shipment of a new drug in interstate commerce based upon a finding that it is unsafe or ineffective or otherwise fails to conform to the standards set up in Section 505(e). Obviously, this purpose is entirely inconsistent with the effect which the court attributes to such withdrawal, *viz.*, that it operates as a condition of the exemption of the drug under Section 107(c)(4).

Thus, the bizarre result of the court's ruling would be that such a drug (including Lutrexin) could become exempt by reason of withdrawal of approval under Section 505(e), whereas the intended effect under the statute is to prevent the shipment of the drug in interstate commerce on the basis of the FDA view that it is still a new drug which does not comply with Section 505.

We submit that a construction so clearly inconsistent with the purpose of the statute should not be allowed to stand.

Our position, and the evidence we have submitted, that Lutrexin was on the market on the day preceding the effective date of the 1962 Amendments (Clause (A) of Section 107(c)(4)) and that it was no longer a new drug on that date because it was then generally recognized as safe (Clause (B)) have not been challenged in this proceeding. In any event, the facts could be determined by FDA at a hearing. We maintain also that Lutrexin meets the test of Clause (C) because it was not covered by an "effective" NDA on that date.

We think it clear that an NDA for a drug which is no longer "new" within the meaning of the Act has no legal effect at all—is not viable in any way. Thus, if FDA purported to approve an application for a drug which was not "new" within the meaning of Section 201(p) the application would not be legally "effective" within the meaning of Clause (C) of Section 107(c)(4).

The Court of Appeals for the Fourth Circuit held in a related case [12] that this argument would make surplusage of Clause (C). It is true, as we have stated, that if a drug which had been NDA'd had ceased to be new on October 9, 1962, it would meet both tests (B) and (C) by reason of that fact.

By the same token, if, as FDA maintains, and the Court of Appeals agrees, every drug which had gone through the new drug procedures and had thereafter ceased to be a new drug was nevertheless "covered by an effective application" within the meaning of Clause (C), then Clause (B) would be surplusage; for if such a drug is "covered by an effective application" despite having lost its new drug status, the test of whether it is no longer a new drug (Clause B) would be useless.

Complementing the basic considerations above discussed is the circumstance that the language of §§ 107(c)(2), (3), and (4) of the Amendments leads clearly to the conclusion that only *new claims* of effectiveness for drugs whose NDAs became effective prior to October 10, 1962, were subject to the amendments. This view is supported by the legislative record of S. 1552, which, as revised, became the 1962 Amendments.

When the bill, as originally reported by the Senate Judiciary Committee, was changed to expand the definition of "new drug" to include drugs not generally recognized as effective, the Committee stated—

> "A question arose as to the circumstances and extent to which a new claim or change of claim of effectiveness made after the initial approval of a new drug application could be made without supporting evidence to be submitted to the Department under the new-drug procedure. In order to eliminate any

[12] *USV Pharmaceutical Corporation* v. *Richardson* (4th Cir., No. 71-1596, May 24, 1972, App. C(2) at 45a.

possible ambiguity on this point the term 'effectiveness' is employed in the committee's substitute amendment." [13]

Likewise, on the floor, Senator Eastland, consistently with the language of Sections 107(c)(2)(3), and (4), said that, with the addition of "effectiveness" to the definition "every brand new product, and every new claim for an existing product, would be subject to the tests and procedures established in § 505 of the Act".[14]

There is nothing inconsistent with these explanations in the history of HR 11581, the companion bill to S. 1552.

It must be clear from the legislative history as well as from the terminology of the 1962 Amendments themselves that (1) the fact that drugs which had never been subject to the new drug procedures were exempt from re-evaluation for effectiveness did not mean that other drugs, such as those which were no longer new drugs on October 9, 1962, were not also exempt and (2) that statements in the Committee Reports and in debate relating to withdrawal of approval of NDAs on the grounds of lack of effectiveness after two years from October 9, 1962, referred only to withdrawal of approval of NDAs for drugs which were still *new drugs* on that date.

(5) Section 107(c)(2) Of The 1962 Amendments

The Court of Appeals for the Fourth Circuit failed to mention a basic argument of HW&D that, under Section 107(c)(2) of the 1962 Amendments, an NDA which was 'effective' on the day immediately preceding the enactment date (i.e. October 9, 1962) is not "deemed approved" and consequently is not subject to withdrawal proceedings under Section 505(e)(3), 21 U.S.C. 355(e)

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[13] S. Rep. No. 1744, Part II, 87th Cong., 2d Sess. 5.

[14] 108 Cong. Rec. 16304 (August 23, 1962).

(3), which is applicable only to NDAs which have been actually approved (or "deemed approved") under the Act.

Under Section 107(c)(3)(B) of the 1962 Amendments, a drug whose application is "deemed approved" under Section 107(c)(2) is not subject to administrative withdrawal-of-approval proceedings under Section 505(e)(3) (lack of substantial evidence of effectiveness) for two years after the enactment date of the amendments.

FDA contended below that Lutrexin was "deemed approved" and approval of its NDA was, therefore, subject to withdrawal under Section 505(e)(3), two years after the enactment date. This theory was cited as legal justification for its withdrawal order (Jt. App. I, 95, 97).

Under the plain language of the statute, however, only those NDA's were "deemed approved" which were "effective" within the meaning of the basic Act on the day preceding the enactment date of the 1962 Amendments (October 9, 1962).

We have stated above our position that the NDA for Lutrexin was no longer "effective" on October 9, 1962, Lutrexin being no longer a new drug. The affidavits of experts which are part of the record state that the drug was generally recognized as safe on that date—the test of whether it was then a new drug. If it was no longer a new drug its NDA no longer had viability—was of no legal effect.

We submit that it is clear that the only drugs "deemed approved" were those which, on October 9, 1962, were still new drugs because they were not then generally recognized as safe.

It should be emphasized that our conclusion that Lutrexin was not "deemed approved" excuses it from administrative withdrawal of approval of its NDA under Section 505(e)(3), but not from judicial proceedings such

as seizure, criminal prosecution and actions for injunctions based on allegations of lack of effectiveness.[15] It is exempt from these judicial proceedings only if it meets the three conditions of Section 107(c)(4) above considered and then only with respect to old claims of effectiveness being made on October 9, 1962.

If scientific developments should result in a re-evaluation by qualified experts and a reversal of their recognition of safety, FDA could proceed in the District Court against the drug on the ground that it had again become a new drug under Section 201(p). Moreover, as we have stated, if the agency believes that the claims of effectiveness for an exempt drug are false or misleading it can proceed against them under Section 502(a) of the Act. There is no exemption from such a proceeding.

FDA is therefore not without effective remedies. The fact that it cannot challenge the status of drugs such as Lutrexin under Section 505(e)(3) with respect to old claims of effectiveness results from a deliberate choice of the Congress.

We submit that these questions of the correct interpretation of basic provisions of the Drug Amendments of 1962, involving as they do the status of hundreds of drugs, should be resolved by this Court. The Court of Appeals, we believe, was clearly wrong in its interpretation of Section 107(c)(4) and in its failure to consider petitioner's argument that Lutrexin (and many other drugs) were not "deemed approved" under Section 107(c)(2). Petitioners and the many other manufacturers of drugs in a position similar to that of HW&D should

[15] Section 505(a), 21 U.S.C. 355(a): "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug." Section 301, 21 U.S.C. 331: "The following Acts and the causing thereof are hereby prohibited: . . . (d) The introduction or delivery for introduction into interstate commerce of any article in violation of section . . . 505."

not have to accept the determination of the Court of Appeals as final. If, in the future, another Court of Appeals should rule differently, many drugs will have been forced from the market so that a decision by this Court would come too late.

Moreover, a serious and basic question of administrative law extending beyond the Federal Food, Drug and Cosmetic Act, is presented here—the authority of an administrative agency to determine its own jurisdiction in proceedings dealing with matters brought before it.

Finally, it is submitted that HW&D, as a participant in new drug proceedings before FDA is entitled, as a part of such proceedings, to a hearing on the facts underlying the jurisdictional questions involved, where, as here, jurisdictional issues have been raised.

CONCLUSION

For the foregoing reasons the cross-petition for a writ of certiorari should be granted.

Respectfully submitted,

EDWARD BROWN WILLIAMS
Counsel for Cross-Petitioner

September, 1972

APPENDIX A

Statutes Involved

Federal Food, Drug and Cosmetic Act

(52 Stat. 1040, as amended, 21 U.S.C. 301 et seq.)

Section 201(p), 21 U.S.C. 321(p), as amended by the Drug Amendments of 1962, P.L. 87-781:

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

Section 502, 21 U.S.C. 352:

A drug or device shall be deemed to be misbranded—

(a) If its labeling is false or misleading in any particular.

Section 505, as amended, 21 U.S.C. 355:

SEC. 505 [355]. (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of

substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to

him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j), or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any

particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

(f) Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28, United States Code. Upon the filing of such petition such court shall have ex-

clusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

The Drug Amendments of 1962, P.L. 87-781, provide in part:

EFFECTIVE DATES AND APPLICATION OF PART A

SEC. 107. (a) Except as otherwise provided in this section, the amendments made by the foregoing sections of this part A shall take effect on the date of enactment of this Act.

(b) The amendments made by sections 101, 103, 105, and 106 of this part A shall, with respect to any drug, take effect on the first day of the seventh calendar month following the month in which this Act is enacted.

(c) (1) As used in this subsection, the term "enactment date" means the date of enactment of this Act; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.

(2) An application filed pursuant to section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date by virtue of paragraph (2) of this subsection—

(A) the amendment made by this Act to section 201(p), and to subsections (b) and (d) of section 505, of the basic Act, insofar as such amendments relate to the effectiveness of drugs, shall not, so long as approval of such application is not withdrawn or suspended pursuant to section 505(e) of that Act, apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested

in labeling covered by such approved application, but shall apply to any changed use, or conditions of use prescribed, recommended, or suggested in its labeling, including such conditions of use as are the subject of an amendment or supplement to such application pending on, or filed after, the enactment date; and

(B) clause (3) of the first sentence of section 505 (e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application (except with respect to such use, or conditions of use, as are the subject of an amendment or supplement to such approved application, which amendment or supplement has been approved after the enactment date under section 505 of the basic Act as amended by this Act) until whichever of the following first occurs: (1) the expiration of the two-year period beginning with the enactment date; (ii) the effective date of an order under section 505(e) of the basic Act, other than clause (3) of the first sentence of such section 505(e), withdrawing or suspending the approval of such application.

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

APPENDIX B

Order and Opinions Below

(1) The Order of the Commissioner of Food and Drugs withdrawing approval of the new drug application for Lutrexin (36 F.R. 11763).

HYNSON, WESTCOTT & DUNNING, INC.

Notice of Withdrawal of Approval of New-Drug Applications

On March 22, 1969, there was published in the FEDERAL REGISTER (34 F.R. 5556) a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new-drug applications for drugs containing lututrin on the ground that there is a lack of substantial evidence that lututrin has the effect or contributes to the effect which the drugs purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Hynson, Westcott & Dunning, Inc., Charles and Chase Streets, Baltimore, Md. 21201, holder of NDA No. 8-986, Lutrexin tablets and NDA No. 10-144, Trexinest tablets by the October 16, 1970 letter of its counsel, has requested a hearing on the following issues:

(1) Whether its lututrin drugs are exempt from the efficacy requirements of 21 U.S.C. 355 under section 107 (c) of Public Law 87-781; (2) whether its lututrin drugs are "new drugs" within the meaning of 21 U.S.C. 321(p)(1); and (3) whether there is a lack of substantial evidence of effectiveness to support the claims made for Lutrexin.

In support of its request for a hearing on the issue of substantial evidence of effectiveness, Hynson, Westcott, and Dunning, Inc. (hereinafter referred to as "HW&D") has submitted a list of its medical documentation previously filed with the Agency, including all data submitted in connection with NDA No. 10-144, correspondence between HW&D officials and the Agency or other persons, labeling for the lututrin drugs, literature articles submitted to the National Academy of Science-National Research Council, and the HW&D letter of August 18, 1969, in which the company first elected to avail itself of the opportunity for hearing.

To support its hearing request on the contentions that HW&D's lututrin drugs are exempt from the efficacy requirements of 21 U.S.C. 355, the company has submitted copies of its pleadings, legal memorandum, exhibits, and affidavits, as well as the transcript and order in Hynson, Westcott and Dunning, Inc. v. Finch (C.A. No. 21112, D. Md., decided Sept. 11, 1970).

The Commissioner of Food and Drugs has reviewed HW&D's request for hearing and the medical documentation submitted, and makes the following findings:

I. *The drugs, their rationale and claims.* a. Lutrexin is labeled as containing 3,000 units of lututrin per tablet. Lututrin is claimed to be a pig uterine relaxing hormone effective in the treatment of functional dysmenorrhea, selected cases of premature labor and threatened and habitual abortion. The package insert claims the drug has demonstrated activity on the living animal uterus, that it relaxes the contracted uterine muscle by direct action thereon, or by blocking pituitary action.

b. Trexinest is labeled as containing 500 units of lututrin and 1.0 milligrams of estrogen, in the form of sodium estrone sulfate, per tablet. Trexinest is recommended for the treatment of menopausal disorders. The

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package insert claims that the combination is more effective than lututrin or estrogen alone and points to lututrin as the responsible agent in the drug's effectiveness.

II. *The applicable regulations.* HW&D's contention that it has an unconditional right to a hearing is denied. The hearing regulations, 21 CFR 130.14, require that a person seeking a hearing set forth specific facts showing the existence of genuine and substantial fact issues which requires a hearing. The order of May 8, 1970 (35 F.R. 7250) granted persons involved in notices of hearing, including HW&D, 30 days in which to amend their requests for hearing to comply with the new regulations. The company was given actual notice on May 19, 1970, that it was required to comply with these regulations in order to properly avail itself of an opportunity for hearing. Applications of the regulations have been upheld by the courts. Pfizer, Inc. v. Richardson, 434 F. 2d 536 (C.A. 2, 1970); Upjohn Co. v. Finch, 422 F. 2d 944 (C.A. 6, 1970); Pharmaceutical Manufacturers Association v. Richardson, 318 F. Supp. 301 (D. Del., 1970). HW&D is bound by the judgment in the last case cited.

III. *The Request for a Hearing*—a. *The issues of exemption under section 107(c) of Public Law 87-781 and under 12 U.S.C. 321(p)(1).* The request for a hearing on these issues is denied. The new-drug applications involved had not been withdrawn prior to enactment of Public Law 87-781. They were "deemed approved" under the 1962 amendments to the Act and are subject to withdrawal on the basis of the effectiveness requirements of the amendments.

b. *Lutrexin and Trexinest are new drugs within the meaning of 21 U.S.C. 321(p)(1).* The conclusions of HW&D's affiants that these drugs are not new drugs cannot be accepted. No adequate and well-controlled clinical investigations published in the medical literature

have been identified. Therefore, there is no data base upon which experts can fairly and responsibly conclude that the safety and effectiveness of the drugs has been proven and is so well established that the drugs can be generally recognized among such experts as safe and effective for their intended uses.

The affiants identify 11 studies as establishing the claims made for the drugs. None purports to be an adequate and well-controlled clinical investigation. They may be summarized as follows:

(1) Majewski and Jennings: Uterine Relaxing Factor for Premature Labor, Ob. & Gyn. 5:649-652 (May 1955); and Further Experiences with a Uterine Relaxing Harmone in Premature Labor, Ob. & Gyn. 9:322-325 (March 1957) by the same authors are one study. The first paper is a preliminary study on 20 patients and the latter is the report on enlarged group of 88 patients. The authors acknowledge that results in the total group are less favorable than in the preliminary study, but conclude that the results are encouraging. Concomitant medication was given an unstated number of patients. There is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced. Nine patients out of 88 in whom the drug proved ineffective were excluded from the report for "statistical reasons". Six patients received the drug for less than 3 hours, which the authors without explanation considered too short a time for a true test of effectiveness. There is no summary or explanation of the statistical methods used in analysis of the data to show that results were not biased or due to chance.

(2) Majewski: Statistical Evaluation in The Reduction of the Incidence of Prematurity (1968) is unpublished. The author claims successful treatment in 86 percent of cases treated in his practice over a 10-year period. Substantiating documentation to establish an

historical control and percentage of patients with medical or surgical complications of pregnancy is not provided. The author acknowledges that some patients with medical complications such as placenta praevia were included in the study. Lutrexin is not claimed to have value in the medical or obstetrical complications of pregnancy which occur in a significant percentage of premature births.

The pairing of live birth percentages by number of pregnancies before and after Lutrexin treatment such as in Table I are all inappropriate. For example, of the 24 cases with one previous pregnancy, 11 live births before treatment and 18 live births after treatment are compared. However, for each of the 18 live births after treatment, an additional pregnancy had elapsed so that the number of previous pregnancies associated with the number 18 is two, not one; as such, the number 18 should be compared with the number 16, the total live births for two previous pregnancies.

The data in Table I does not admit of statistical evaluation by the chi-square test since the test is based on the assumption that each number in the columns of Table I is the sum of independent yes or no responses, e.g., for the one patient with seven previous pregnancies, four live births are correlated, thus ignoring the sample size of one and using an erroneous sample size of four.

(3) Rezek: The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luterum in the Treatment of Dysmenorrhea, Am. J. Ob. & Gyn. 66:396-402 (August 1953). The report does not state the method of patient selection, nor does it indicate comparability of pertinent variables such as severity or duration of diseases. Concomitant medication is not excluded. No explanations of the methods of observation, the recording of results, and steps taken to minimize patient and in-

vestigator bias are provided. The historical controls employed are inappropriate.

(4) Rezek: Lutrexin in the Treatment of Premature Labor, Ann. N.Y. Acad. Sci. 75:995-997 (January 1959). The method of selection of the patients does not show progressive dilation of the cervix, which is necessary to accurately diagnose premature labor. The methods of observation and the recording of results are not explained. No statistical evaluation was presented to show that results claimed are significant in terms of the patient population.

(5) Gratton: The Treatment of Infertility and Prematurity Pregnancy Problems (1968) is unpublished. Patients received numerous concomitant therapies until the fifth month of pregnancy which prevents scientific attribution of results to lututrin therapy. The method of patient selection is unexplained.

Statistically the study lacks adequate design and evaluation. There is no showing that the cases studied are representative of the population to which inferences are made. The pairings of live births percentages in Table II cannot be compared since the number of previous pregnancies differs between the pair percentages and there is no data on possible etiologic factors of previous abortions and premature labor.

(6) Gray: Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases (undated) is an unpublished report on 15 selected cases the author has treated. No plan or protocol is provided to allow determination of the objectives of the study, the method of patient selection, diagnostic criteria of the condition to be treated, laboratory tests to be made, the methods of observation and recording of results. The author's review of his records does not constitute an adequate and well-controlled investigation.

(7) Four papers by Dr. Trythall were listed in the attachment to his affidavit. In only one article is lutrexin ever mentioned.[*] The three sentences devoted to the drug provide no information whatsoever except that the author claims to have found it effective in his practice.

The affiants state that double blind investigations of lututrin are unethical because the drug is effective and complications of pregnancy may be life-threatening. The Commissioner does not reach that issue, since none of the historically controlled studies relied upon were adequate and well-controlled investigations.

There are other reasons why HW&D's medical data lack merit, but in view of the above finding their delineation is unnecessary.

c. *The issue of substantial evidence of effectiveness.* The request for a hearing on this ground is denied. The regulations, 21 CFR 130.14, require HW&D to submit a well organized and full factual analysis of the clincial and other investigational data it is prepared to prove at a hearing. The request must set forth specific facts showing that there is a genuine and substantial issue of fact requiring a hearing. HW&D has not attempted compliance with these requirements.

Rather than identify and discuss the efficacy data relied upon to support the claims made for its drugs, the company has merely provided a list, extending to four pages, of practically all materials ever submitted to the Agency and the NAS-NRC. The materials are described, for the most part, in general terms (e.g., "data submitted in connection with New Drug Application for Lutrexin tablets * * *, Lutrexin bibliography * * *, Trexinest bibliography * * *, reprints and abstracts * * *). What the Commissioner is required to do is

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[* Lutrexin is in fact discussed in two of the papers (Jt. App. II, 64 and 68)].

determine from this material, what HW&D may or may not consider relevant and, therefore, relies upon. In the case bibliographies, the Commissioner would be required to research each article and then determine if it is relevant, or whether HW&D might consider it relevant. Because such a procedure is not contemplated by the regulation, the request for hearing is denied for failure to comply with applicable regulations.

Apart from the refusal of HW&D to comply with 21 CFR 130.14, the most basic material in the Lutrexin new-drug application reveals a lack of adequate and well-controlled investigations showing that lututrin will have the effect HW&D claims for it.

The only evidence submitted that lututrin may have biological activity in humans when taken orally is a test on nine women by Jones and Smith in which positive results were reported to have been obtained in six subjects. No plan or protocol was stated. No data on the participating patients was provided. No explanation of procedures for patient selection, or criteria for inclusion in the study, or appropriate laboratory tests before and after administration of lututrin was provided. No statistical analysis showing the test population was of significant size or that results obtained were significant is shown. Moreover, there is no evidence that results claimed have ever been reproduced in humans by other investigators.

Therefore, the Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1053, as amended; 21 U.S.C. 355(e)), and under the authority delegated to him (21 CFR 2.120), finds that on the basis of new information before him with respect to each of said drugs, evaluated together with the evidence available to him when each application was approved, there is a lack of substantial evidence that each of the drugs will have the

effects it is purported or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof.

Pursuant to the foregoing findings, approvals of the above new-drug applications, and all amendments and supplements thereto, are withdrawn effective on the date of the signature of this document.

Dated: May 31, 1971.

CHARLES C. EDWARDS
Commissioner of Food and Drugs

[FR Doc. 71-8557 Filed 6-17-71; 8:46 am]

APPENDIX B

(2) Opinion of the United States Court of Appeals for the Fourth Circuit, CCH Food, Drug, Cosmetic Law Reporter, ¶ 40,666.

UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 71-1717

HYNSON, WESTCOTT AND DUNNING, INCORPORATED,
Petitioner,

—versus—

ELLIOT RICHARDSON, Secretary of Health, Education and Welfare and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Respondents.

On Petition to Review an Order of the Commissioner of Food and Drugs

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(Argued February 7, 1972. Decided May 24, 1972.)

Before BUTZNER, RUSSELL and FIELD, Circuit Judges

RUSSELL, CIRCUIT JUDGE:

The appellant, a drug manufacturer, seeks review of a final order withdrawing marketing approval (NDA) of the drug Lutrexin by the Commissioner of Food and Drugs, Department of Health, Education and Welfare.[1] The appellant alleges error in such order of withdrawal (1) for failure to sustain its claim of exemption from

[1] Section 355(h), 21 U.S.C.

withdrawal on account of lack of "substantial evidence" of effectiveness of its drug and, if this claim of exemption is overruled, (2) for denial of a hearing, as required under the applicable statute, on its showing of effectiveness. We reverse.

The appellant was granted an approved NDA for Lutrexin in 1952 [*sic*]. At that time, the Food, Drug and Cosmetic Act of 1938 conditioned such grant on general recognition of safety of the drug approved. In 1962 the Act was amended to authorize withdrawal of an approved NDA for any drug for which the Commissioner "after due notice and opportunity for hearing", found there was "a lack of substantial evidence of effectiveness.[2] The term "substantial evidence" was defined in the Amendments as "consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[3] There was an exemption from these requirements for drugs, which, *inter alia*, were not covered on the day immediately before the enacting date of the Amendments (i.e., October 9, 1962) by an "effective NDA".[4]

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[2] Section 355(e), 21 U.S.C.

[3] Section 355(d), 21 U.S.C.

[4] In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force * * *, and (C) was not covered by an effective application under section 505 of that Act * * *, the amendments to section 201(p) * * * made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day." Section 107(c)(4), appended to Section 321, 21 U.S.C., 1972 Supplement, p. 192.

In carrying out his new responsibilities under the Amendments, the Commissioner secured the services of the National Academy of Sciences-National Research Council (NAS-NRC) for reviewing the claims of effectiveness on behalf of any drugs NDA'd between 1938 and 1962.[5] To facilitate its assignment, NAS-NRC set up a Drug Efficacy Study Group and all drug manufacturers with approved NDAs obtained between 1938 and 1962 were directed by the Commisioner to submit to this Group evidence "pertinent to the evaluation of the effectiveness of the(ir) drugs."[6] The appellant submitted to the Group clinical data, investigations and studies in support of the effectiveness for its drug Lutrexin. After considering such data, NAS-NRC concluded that Lutrexin was "possibly effective" but indicated the supporting documentation was inadequate. The Commissioner advised the appellant of his concurrence with the conclusions of NAS-NRC and, as required by the statute, extended to it an opportunity for a hearing on the proposed withdrawal of the approved NDA for Lutrexin.[7] At such a hearing, the appellant was advised it might "produce evidence and arguments why approval * * * should not be withdrawn."[8] The appellant in due time requested such hearing. Under the Commissioner's regulations, a hearing was required within 90 days after such request, unless the parties agreed otherwise.[9] However, although no delay was agreed on, hearing within such period was not had. The delay on the part of the Commissioner in setting a hearing was due to litigation over the procedure to be followed by it in implementing its efficacy review and in conducting hearings resulting

[5] 21 F.R. 13014, October 6, 1966.

[6] 21 F.R. 13014.

[7] 33 F.R. 7701.

[8] 34 F.R. 5556.

[9] 21 C.F.R. 130.14(b).

therefrom.[10] It is unnecessary to review the difficulties encountered in developing valid regulations for such hearings. It is sufficient for the issues here that it was not until May 8, 1970, that the legal objections to the regulations were finally resolved. During this interregnum when the regulations of the Agency were under challenge and the Commissioner was delaying a hearing, the appellant, whose request for a hearing had been delayed for more than a year, sought in District Court a declaratory judgment to the effect that, under the exemption clause included in the 1962 Amendments, Lutrexin was not a "new drug" on and before October 10, 1962, and was thereby exempt from the requirement of evidence of effectiveness under the Amendments. Such action was dismissed on the ground that primary jurisdiction to resolve the issue of exemption under the Act rested with the Commisioner. No appeal was taken from this dismissal.

While this declaratory action was pending, the Commissioner issued his new regulations detailing the circumstances under which an applicant might secure a hearing on a proposal by the Commissioner for withdrawal of an effective NDA. By these regulations, the Commissioner was authorized to deny a hearing, "When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such

[10] See *Pharmaceutical Manufacturers Association* v. *Finch* (D.C. Del. 1970) 307 F. Supp. 858; *Upjohn* v. *Finch* (6th Cir. 1970) 422 F.2d 944; and *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F.2d 586.

data".[11] After the regulation had been legally promulgated, which was more than a year after the appellant had requested a hearing, the Commissioner directed the appellant's attention to these new regulations and suggested that it amend its request for a hearing to comply. Though it contended it had, by its earlier request, perfected its right to a hearing and was not obligated to amend its request, the appellant did, following the dismissal of its declaratory action, submit a considerable amount of clinical medical studies and investigations in support of the claim of effectiveness for its product by way of compliance with the new regulations. The Commissioner, however, dismissed the appellant's request for a hearing on the basis of such showing, finding (1) that its drug was a "new drug" requiring proof of effectiveness, and (2) that its showing of effectiveness was insufficient to demonstrate a "genuine and material issue of fact" under the test of "substantial evidence" as defined in the Amendments. On the basis of these findings it withdrew the approved NDA for Lutrexin. It is from this order that appeal has been taken.

I

The appellant's claim to an exemption for its drug is easily disposed of. We have held in a related case that a drug covered by a pre-1962 approved NDA, which had not been withdrawn under the procedure set forth in Section 505(e), is not entitled to the exemption granted under Section 107(c)(4) of the Amendments.[12] The appellant's NDA was outstanding and had not been legally withdrawn on October 10, 1962. It cannot accordingly claim the benefit of the exemption statute for its drug. While the appellant was entitled to have this issue resolved by the District Court, it was not prejudiced by, and cannot complain of, the refusal by the District Court

[11] 21 C.F.R. 130.14(b).

[12] *USV Pharmaceutical Corp.* v. *Richardson*, (4th Cir. 1972) —— F.2d ——.

to exercise jurisdiction. Nor, for that matter, did the appellant appeal and is accordingly without standing in this proceeding to challenge that dismissal.

II

The crucial issue in this case, however, is posed by the appellant's second contention and revolves about the requirement in the Act that, before the entry of a final order of withdrawal, the applicant be given an "opportunity for hearing". At such a hearing, the procedure adopted by the Commissioner allows the applicant to "produce evidence and arguments to show why approvals of (its drugs) * * * should not be withdrawn." [12a] Of course, the Commissioner might, as he did by his regulations issued in 1970, provide for the denial of a hearing where it clearly appeared from the applicant's own showing there was no "genuine and substantial issue of fact" on which the claim of the applicant might be sustained. *Ciba-Geigy Corp.* v. *Richardson* (2d Cir. 1971) 446 F. 2d 466, 468. It may be assumed that such regulation, when issued will apply to all pending applications. *U. S.* v. *Storer Broadcasting Co.* (1956) 351 U.S. 192, 205. But, in applying this regulation and in making his determination thereunder, the Commissioner's discretion is not absolute. Neither due process nor the Administrative Practice [*sic*] Act permits an arbitrary denial in any case where it can be fairly said there are "genuine and substantial issues of fact" in dispute.[13] Such

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[12a] Whether this is too narrow and improperly confines the scope of the hearing, so far as it is adjudicatory, see Davis, *The Requirement of a Trial-Type Hearing*, 70 Har. L.Rev. 193 (1956).

[13] See *Ciba-Geigy Corp.* v. *Richardson, supra*, at p. 468. The question is analogous to that presented by a demand for a hearing in connection with an N.L.R.B. election where the right to a hearing subject to the same general limitations as stated in the Commissioner's regulations, and it would seem the same test of the right to a hearing is applicable. For the rule in such N.L.R.B. case, see *N.L.R.B.* v. *Bata Shoe Co.* (4th Cir. 1967) 373 F.2d 821, 825-6; *United States Rubber Co.* v. *N.L.R.B.* (5th Cir. 1967) 373 F.2d 602, 606; *N.L.R.B.* v. *Smith Industries, Inc.* (5th Cir. 1968) 403 F.2d 889, 892-5.

a denial would, in addition, be violative of the Congressional purpose expressed in the provision for a hearing. And the courts must see that such Congressional purpose is not thwarted by administrative usurpation; or, as the Court said in *Environmental Defense Fund, Inc.* v. *Ruckelshaus* (D.C.C.A. 1971) 439 F. 2d 584, 596, the courts have "an obligation to ensure that the administrative standards conform to the legislative purpose * * *." Accordingly, only if it can be fairly said that the clinical tests and medical studies and investigations submitted by the applicant, if credited and accepted, will not support a finding that they provide "substantial evidence" of effectiveness was it proper for the Commissioner to deny the appellant a hearing *before* entering a final order of withdrawal. The judicial test is somewhat the converse of that to be applied in a review of a decision of the Commissioner entered *after* a hearing. In that instance, his decision is to be upheld, if sustained by any substantial evidence.[14] But in determining whether the Commissioner acted within the limits of his discretion on the procedural question of whether a hearing is to be allowed, the test is whether there is any "genuine and substantial" evidence that supports the position of the applicant. Manifestly, the applicant does not have to satisfy or convince the Commissioner by his evidence that his product is effective as a predicate for securing his right to a hearing. If that was his burden, a hearing would never be necessary or appropriate. If he, by his showing, convinced or satisfied the Commissioner, the proposed withdrawal would naturally be denied; on the other hand, if he failed to satisfy, then the Commissioner would deny a hearing and order withdrawal. In either event, a hearing would be useless and the Congressional promise of a hearing would be purely illusory. No such exacting standard of proof is required as a basis simply

[14] Section 355(h), 21 U.S.C.

for the right to be heard; as has been observed, all that is required for securing a right to a hearing is that the showing be such that, if accepted, a finding of "substantial evidence" of effectiveness would be supportable. And "substantial" in this connection does not mean "preponderant evidence" or "conclusive evidence". Congress specifically discarded those terms for the milder term "substantial", which was understood to embrace the idea, not of a preponderance but rather of a responsible body of qualified opinion.[15]

Applying the foregoing principles, we are of opinion the showing of the appellant was such that, under a reasonable construction of the Commissioner's own regulations, as well as under familiar principles of due process, and the requirements of the Administrative Procedure Act, it was entitled to an impartial hearing before its NDA was withdrawn. It must be noted that no qualified expert has given an opinion that Lutrexin is in-

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[15] In the course of committee deliberation a distinction evolved . . . between two tests—the "preponderant evidence" test and the "substantial evidence" test as now specifically defined. Under the former a claim would not be accepted under the new drug section unless it represented the preponderant view of experts . . . the committee recognizes that in the difficult area of drug testing and evaluation there will frequently, if not usually, be a difference of responsible opinion. The committee feels the existence of such a difference should not result in disapproval of a claim of effectiveness if it is supported by substantial evidence defined in the manner set forth below [that is adequate and well controlled investigations by qualified experts upon the basis of which conclusions made [*sic*] be fairly and responsibly drawn.].

[Application of the substantial evidence test means that] a claim could be rejected if it were found (a) that the investigations were not "adequate"; (b) that they were not "well-controlled"; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which its application is made; or (d) that the conclusions to be drawn by such experts could not fairly and responsibly be derived from their investigation.

S. Rep. No. 1744, 87th Cong., 2nd Sess. Part II, pp. 5-6, and see, 2 U.S. Code Congress. & Administrative News, 87th Cong., 2d Sess., p. 2892 (1962).

effective for the uses intended. The NAS-NRC review concluded it was "possibly effective". Neither is there any contention that it is unsafe when used for the purposes intended. The real basis for the determination by the Commissioner that the appellant had failed to make a showing of any genuine issue of fact on the effectiveness of its drug was the conclusion that the various scientific articles and tests submitted by the appellant were not "adequate and well-controlled clinical investigations" within the statutory definition of "substantial evidence". In his decision, the Commissioner sought to point out the deficiencies in the investigations submitted by the appellant which justified this conclusion. In so doing, he did not impugn the competency or qualifications of the scientists and medical experts whose investigations were cited by the appellant in support of its claim. Their professional qualifications, as they appear in the record, are impressive. Their investigations and opinions, some of which have been published in recognized professional medical journals, are, however, dismissed by the Commissioner with the statement that, "No adequate and well-controlled clinical investigations published in the medical literature had been identified". In making that statement, he disregards the categorical opinion of his former Director of the Bureau of Medicine and Medical Director that the clinical tests and investigations submitted by the appellant represented " 'well-controlled' clinical studies". He proceeds to fault two investigations published in an authoritative medical journal, submitted by the appellant, because, "There is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced", and "There is no summary or explanation of the statistical methods used in analysis of the data to show that results were not biased or due to chance". Another unpublished investigation is dismissed because, "Substantiating documentation to estab-

lish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided". Two published studies by a clinical professor of Obstetrics at the University of Illinois are criticized, in one instance, because "The report does not state the method of patient selection" and "Concomitant medication is not excluded" and, in the other, because "The method of selection of the patients does not show progressive dilation of the cervix, which is necessary to accurately diagnose premature labor." Assuming that all the objections by the Commissioner to these clinical studies, conducted as they were by competent medical authorities, may have some validity, they do not justify a final conclusion, made *ex parte*, without a hearing, that it "clearly appears" that there is no genuine issue of fact on the effectiveness of Lutrexin, which is the test under the Commissioner's own regulation for denial of a hearing; at most, they merely create a genuine question of fact to be resolved at a hearing upon proper evidence. Whether the studies were as controlled as they might have been and whether there was a failure in these studies as published to fill in all the details the Commissioner might think appropriate are matters that could be developed at a hearing, after the authors were examined and the reliability of the investigations further inquired into.

The order of the Commissioner, from which this appeal is taken, is set aside for failure to provide the petitioner with an "opportunity for a hearing" before the entry of said order.

REVERSED.

APPENDIX C(1)

Opinions In Related Cases

UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 71-1243

BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMACEUTIAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC., SOUTHERN DRUG & MFG. CO., THE BLAINE COMPANY, BROWN PHARMACEUTICAL CO., MAYRAND, INC., PHARMACEUTICAL ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHARMACEUTICALS, INC., BCR PHARMACAL CO., INC., ALTO PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES, INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMACEUTICALS PRODUCTS, INC., FOS PHARMACEUTICAL CO., W. E. BOODY & CO.,

Appellants,

—versus—

ELLIOT P. RICHARDSON, SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION,

Appellees.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF SOUTH CAROLINA, AT GREENVILLE. ROBERT W. HEMPHILL, DISTRICT JUDGE.

(Argued December 8, 1971 Decided May 23, 1972)

Before WINTER, RUSSELL and FIELD, Circuit Judges

RUSSELL, CIRCUIT JUDGE:

This appeal turns on a construction of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1962.[1] 21 U.S.C. 301, *et seq.* This statute requires pre-marketing approval and clearance of any "new drug" by the Secretary of Health, Education and Welfare.[2] The term "new drug" is defined as one "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof * * *."[3] From a denial of a pre-marketing approval or a withdrawal of a previously given approval, an appeal, originally to the District Court, now

[1] There was an earlier Food and Drug Act of 1906. 34 Stat. 768 (1906). It did not provide for any pre-marketing review of the safety of drugs. The sulfanilamide episode in 1938 prompted the enactment of the Federal Food, Drug and Cosmetic Act of that year to replace the earlier Act and to provide, *inter alia*, for such pre-marketing review of "new drugs". See C. W. Dunn, *Federal Food, Drug and Cosmetic Act—A Statement of Its Legislative Record*, pp. 1316-27 (1938). The fears generated by the thalidomide tragedies gave the impetus for the Amendments of 1962. See Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, 185 at p. 191, n. 45 (1971).

[2] Section 355(a), 21 U.S.C.

The actual approval of a "new drug" under the Act is normally processed by the Food and Drug Administration (FDA) in the Department of Health, Education and Welfare (HEW), and the approvals, when granted, are generally referred to as New Drug Approvals (NDAs). FDA, when used herein, refers to the Food and Drug Administration, and NDA is intended to describe an approval by FDA of a "new drug" application under the Act.

[3] Section 321 (p) (1), 21 U.S.C.

See, also, *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F. Supp. 443, 445, n. 2:

> "The statutory definition of the phrase 'new drug' controls this case, regardless of any other meaning attributable to the phrase or to the word 'new' by common understanding or other authority."

to the Circuit Court of Appeals, is authorized.[4] Drugs, which do not fit the definition of a "new drug" do not require FDA clearance for marketing. There is no provision in the Act for administrative determination whether a particular drug is a "new drug" nor for any right of appeal from any such determination. The FDA sometimes offers to render "informal advice" as to whether it considers a product a "new drug" but it uniformly designates such opinion "advice." [5] Accordingly, the responsibility for determining whether its product is a "new drug," requiring pre-marketing clearance by FDA, rests on the manufacturer, who must act at its peril.[6] If it makes an incorrect determination and seeks to market without FDA clearance a drug meeting the definition of a "new drug," it lays itself open to drastic judicial procedures that may be invoked by FDA, i.e.: The product may be seized in an *in rem* action instituted by the Government; [7] its sale may be enjoined in an action begun by the Government; [8] in addition, the manufacturer may be subjected to criminal action.[9] All these remedies must be prosecuted in the District Court and the role of the Secretary is that of plaintiff or prosecutor. The Act thus establishes two forum for the regulation of drugs: One is administrative and deals with the procedures for securing pre-marketing clearances for the statutorily defined "new drug," with right of appeal from a denial of

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[4] Section 355(h), 21 U.S.C.

[5] 21 C.F.R. 130.39.

[6] Cf. *United States* v. *Dotterweich* (1943) 320 U.S. 277, 281, where, speaking of the Act of 1938, the Court said:

> "In the interest of the larger good it puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger."

[7] Section 334, 21 U.S.C.

[8] Section 332, 21 U.S.C.

[9] Section 333, 21 U.S.C.

approval, or withdrawal of a previous approval, to the District Court, later changed to the Court of Appeals; the other is judicial and is intended to make effective and give strength to the requirement that "new drugs" be cleared as safe before marketing by providing the Government with certain potent judicial remedies, *available exclusively in the District Court.*

Under the 1938 Act, a new drug was one "not generally recognized by experts * * * as safe for its intended use." The Amendments added "effectiveness" as well as "safety" to the definition. Simply stated, the change effected by the Amendants was that, whereas prior to the 1962 Amendments a drug which was generally recognized as safe was not a "new drug," the Amendments defined a drug as "new" if it were not generally recognized as both safe *and effective.* Furthermore, they replaced the provision for automatic approvals of applications not disapproved within a fixed time with a requirement of a positive act of approval on the part of FDA.[10] They proceeded to provide that the Secretary must find as a basis for clearance of a new drug not only safety but "substantial evidence" of effectiveness, consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." The applicability of these amendments, including the revised definition of "new drug" to drugs already marketed, either under previously issued NDAs, or as "old drugs" requiring no FDA approval, was carefully spelt out in the Amendments and certain "grandfather rights" were granted. For all previously NDA'd drugs, the Amendments conferred a grace period of two years after the effective date of the Amendments within which to prepare evidence to satisfy the new requirement of efficacy added by the revised definition of "new drugs";

[10] Section 355(c), 21 U.S.C.

during that "transitional" period no revocation or withdrawal of approval because of a lack of substantial evidence of efficacy of such drugs was permitted.[11] For a drug, however, which on the day prior to the enactment of the Amendments was (1) being "commercially used or sold in the United States," (2) "was not a new drug as defined by" the pre-Amendment statute and (3) "was not covered by an effective (new drug application, * * *" "on the day immediately preceding the enactment date" of the Amendments, there was a permanent exemption from the efficacy provisions of the Amendments so long as the drug's labeling remained the same.[12] In summary, these provisions required that, "Those drugs which had obtained effective NDAs must be proven efficacious after two years; those which had not need never be proven efficacious so long as they had become safe prior to the 1962 Amendments." [13]

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[11] Section 107(c)(3), P.L. 87-781, Section 321, Supplement 1972, 21 U.S.C.

[12] Section 107(3)(4), P.L. 871-781, Section 321, 1972 Supplement, 21 U.S.C.; see, also, *Tyler Pharmacal Distrib. Inc.* v. *U.S. Dept.* v. *Health, E. & W.* (7th Cir. 1969) 408 F. 2d 95, 99.

It should be noted that Section 321(p)(1) provides a "grandfather clause" applicable to pre-1938 drugs. This clause is not relevant to this action, which is concerned with drugs introduced between 1938 and 1962, and the subsequent references to "grandfather clause" in this opinion are to section 107(c)(4).

[13] Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, p. 196 (1971).

See, also, *United States* v. *Allan Drug Corp.* (10th Cir. 1966) 357 F. 2d 712, 719, note 9, quoting from the Supplemental Report of the Senate Committee on Drug Amendments of 1962, as set forth in the notes to Section 321, 21 U.S.C.:

> "Thirdly, in the case of a drug on the market which was never subject to the new-drug procedure before, the amendments to the new drug definition relating to drug effectiveness would not apply to existing labeling claims."

In the Conference Report of the House Managers on the Amendments, it was stated that the Amendments included "the Senate lan-

The "grandfather clause" set forth in Section 107(c)(4) simply continues for the products satisfying its criteria the pre-1962 definition of a "new drug". Its effect is to assure that a drug which was generally recognized by qualified experts as safe for the purposes recommended for its use on October 9, 1962, need not be NDA'd as *effective* under the new requirements for the issuance of an NDA as a "new drug". But any drug, whether requiring an NDA or not, whether a "new drug" or an "old drug", is subject to the misbranding provisions of the Act and may be proceeded against on that basis. A false claim of either safety or effectiveness constitutes misbranding, rendering a drug subject to both civil and criminal penalties. *United States* v. *Article of Drug Labeled Decholin* (D.C.Mich. 1967) 264 F. Supp. 473, 482-3; *United States* v. *Lanpar Company* (D.C.Tex. 1968) 293 F. Supp. 147, 153-4.[14] Accordingly, in *United States* v. *Guardian Chemical Corporation* (2d Cir. 1969) 410 F. 2d 157, a drug manufacturer was acquitted of a charge of marketing a "new drug" without securing an NDA, but was convicted under a separate count of the indictment charging misbranding. "Thus", as one commentator has aptly stated, "the amplications of the FDA's authority (as granted by the 1962 Amendments)

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guage providing with respect to existing label claims of drugs that have never previously been subject to the new-drug procedure substantially the same savings provisions as the corresponding provision of the House bill (Section 197(d))." *U. S. Code Congressional and Administrative News*, 87th Congress, 2d Session (1962), p. 2932. Again, in H.R. Rep. # 2526, p. 23, it is stated that the exemption granted by the "grandfather clause" applies "to existing claims of drugs that have never been subject to the new-drug procedure".

[14] See, also, *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 548:

> "A good case could certainly be made that, quite apart from this, the 'efficacy' of a drug is necessarily related to the use recommended."

is (was) not due to the absence of power to proceed against ineffective drugs, but rather to authorize the exercise of that power at the initial stage, that is, *before* marketing, and also to shift the burden of proof to the applicant." Jurow, *The Effect on the Pharmaceutical Industry of the "Effectiveness" Provisions of the 1962 Drug Amendments*, 19 Food, Drug, Cosmetic Law Journal, 110, at p. 116 (1964).[15]

The plaintiffs, manufacturers of a prescription drug containing pentylenetetrazol and nicotinic acid, claim the protection of the "grandfather clause" included in Section 107(c)(4) for their products and that contention represents the substantive issue in this case. It is undisputed that plaintiffs had marketed their product commercially for many years prior to and on October 9, 1962,[16] without an NDA under the claim that it was not a "new drug" within the definition of the Act, and therefore required no NDA. Such claim was supported, it is asserted, both by previous informal advice of the Secretary and by the general recognition of the safety of such product by "experts qualified by scientific training and experience" to make such evaluation. The defend-

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[15] See, also, Senate Report # 1744, *U. S. Code Congressional and Administrative News*, 87th Cong., 2d Sess. (1962), pp. 2892 and 2893, where, in justifying the Amendments, it is stated:

> "* * * where a drug is essentially innocuous, it (FDA) must clear the drug despite the fact that its claim of effectiveness is not borne out by the evidence. In such cases the Food and Drug Administration may proceed against the drug manufacturer by seizure of the drug for misbranding. However, the Department believes that the manufacturer should satisfy the Food and Drug Administration that his product is effective for the purposes claimed before it is marketed. * * * No question of safety is involved, and the Food and Drug Administration presently has ample power, including seizure, to proceed against any safe drug for which unsupported claims of effectiveness are made."

[16] This was the day "immediately preceding the enactment date" of the Amendments of 1962.

ants, the Secretary of HEW and the Commissioner of Food and Drugs, in their brief, concede that "Over the years since 1938" and until 1968, the Food and Drug Administration had given the opinion that certain pentylenetetrazol combinations similar to those of the appellant were not "new drugs." [17] Moreover, the District Court observed in its opinion that there was "no contention (by the FDA) that the use of the plaintiffs' drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs." On this basis, the plaintiffs contended that they met exactly the criteria established for exemption from the requirements of general recognition by qualified experts of the effectiveness of their products as provided in the permanent grandfather section of the 1962 Amendments.

Prior to the filing of this action, however, the defendants withdrew their advice that products such as those distributed by the plaintiffs were "old drugs" and contended that such products did not qualify for exemption under the "grandfather clause," Section 107(c)(4). The basis for this contention was the claim (1) that these drugs were not generally recognized by qualified experts as safe as of the effective date of the Amendments of 1962 and (2) that they were "me-too" drugs, whose marketability without FDA clearance depended in turn on the NDAs granted the basic drug, and for that reason must be regarded as covered by an effective NDA on the

[17] It is, of course, axiomatic that such opinions or advice can create no estoppel against the Government. *AMP Incorporated* v. *Gardner* (D.C.N.Y. 1967) 275 F. Supp. 410, 412, n. 1, aff. 389 F. 2d 825, cert. den. 393 U. S. 825, reh. den. 395 U. S. 917. The most that can be claimed for such opinions is that they lend color and good faith to the plaintiffs' claims. FDA not only has the right but is obligated to change its opinion if it learns its prior position was erroneous. *United States* v. *60 28- Capsule Bottles, More or Less, etc.* (D.C. N.J. 1962) 211 F. Supp. 207, 215, aff. 325 F. 2d 513.

effective date of the Amendments.[18] Faced with this threat, the plaintiffs began this action for a declaratory judgment sustaining their right to exemption from proof of the effectiveness of their product and for injunctive relief awaiting the disposition of their claim for exemption. The defendants directed against the complaint a motion to dismiss or for summary judgment, which, in essence, (1) asserted primary jurisdiction in the Secretary to determine whether the products of the plaintiffs met the requirements for exemption under Section 107 (c) (4), particularly whether they were "new drugs," requiring pre-marketing approval under the Act, (2) denied the propriety of a declaratory judgment action, and (3) claimed that the products of the plaintiffs were "new

[18] The defendants assert that three "new drug" applications filed by other manufacturers and earlier approved by the FDA covered drugs similar in every particular to those marketed by the plaintiffs. Proceedings for withdrawal of the approval of such "new drugs" had been begun by FDA in advance of the filing of this action. In fact, such proceedings to a large extent prompted this action. It is the contention of the defendants that the withdrawal of what they describe as "the primary NDAs" operates to remove the marketability from what they assert are the "me-toos" or non-NDA'd drugs which are similar to other drugs which have secured effective NDAs. The plaintiffs deny that their drugs are like those previously NDA'd. They argue that those NDA'd products, unlike theirs, are intravenously administered or are a compound containing, in addition to the components of plaintiffs' drugs, reserpine. Such changes in formula or method of administering vitiated any claim by their manufacturers that they were marketing an old drug and required an approval as a new drug. The plaintiffs assert their drugs are not subject to any such disability. These, however, are questions of fact not relevant to the simple question of jurisdiction presented by this appeal and may be inquired into on remand. Even if the products of the plaintiffs be deemed "me-too" drugs (i.e., simply "a copy of a pioneer drug which preceded it on the market"), it is by no means clear that they do not "meet the requirements for section 107 (c) (4) protection" and the argument of the Government to the contrary has been described as "lacking in merit." See, Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown Law Journal, 185 at p. 203-207 (1971); Hagan, *Grandfather Protection under the Drug Amendments of 1962*, 19 Food Drug Cosmetic Law Journal, 119, at p. 125 (1964).

drugs" which did not qualify for exemption under the "grandfather clause."

The District Court sustained the right of the plaintiffs to maintain a suit for a declaratory judgment and the jurisdiction of the Court in such action to determine judicially whether the products of the plaintiffs were "new drugs," on the effective date of the Amendments, and whether they were or were not entitled to the benefits of the "grandfather clause."[19] However,—and this is the nub of the controversy between the parties on this appeal —it concluded that the Secretary had concurrent jurisdiction to determine whether plaintiffs' products were "new drugs," requiring pre-marketing clearance, and that, because of the greater expertise of the Secretary in the field, it deferred to the Secetary's assumed jurisdiction to determine whether the drugs of the plaintiffs came within the exemption provided by the "grandfather clause." It enjoined any action against the plaintiffs and their products until the plaintiffs had been accorded a hearing before the Secretary on the issue of the qualifications of these drugs for protection under the "grandfather clause." It is the conclusion of concurrent jurisdiction in the Secretary and deference to that assumed concurrent jurisdiction from which the plaintiffs have prosecuted this appeal.

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[19] In support of the right of the plaintiffs to maintain a suit for declaratory judgment, the District Court relied on *Abbott Laboratories* v. *Gardner* (1967) 387 U. S. 136 and the companion case of *Toilet Goods Assn.* v. *Gardner* (1967) 387 U.S. 158. Additional support for such right is found in *AMP, Incorporated* v. *Gardner, supra; Durovic* v. *Richardson* (D.C. Ill. 1971) 327 F. Supp. 386; *Lemmon Pharmacal Co.* v. *Richardson* (D.C. Pa. 1970) 319 F. Supp. 375. The right of the Court to determine the applicability of the "grandfather clause" is equally clear and has been sustained in *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F. Supp. 443, 445; and *United States* v. *Article Consisting of 36 Boxes, etc.* (D.C. Del. 1968) 284 F. Supp. 107, 112, n. 13, aff. 415 F.2d 369.

The defendants, on the other hand, have not cross-appealed and have accordingly acquiesced in the decision of the District Court that the action is properly maintainable as a declaratory judgment proceeding under Section 2201, 28 U.S.C. and that the District Court has jurisdiction over the substantive issue in this case, i.e., whether plaintiffs' products are "new drugs," as defined in the Act. The question in the case is thus whether the Secretary has concurrent jurisdiction to determine whether a drug is a "new drug" under the Act or whether that issue is cognizable only in the District Court. Contrary to the conclusion of the District Court, we conclude that the Act confers no such jurisdiction on the Secretary and, therefore, no basis for any deference by that Court to the concurrent jurisdiction of the Secretary.

The FDA has neither primary jurisdiction, as the defendants argue, nor concurrent jurisdiction, as the District Court concluded, to adjudicate whether a product is an old or new drug. It may, in its prosecutorial role, reach a conclusion that a product being marketed is a "new drug" requiring pre-marketing approval; but that opinion is not adjudicatory, it is only the basis on which the FDA, as the prosecutor or initiator of either a seizure or injunctive action in the District Court, may invoke the jurisdiction of that Court to determine, among other issues, whether the drug challenged is a "new drug." There is manifestly no provision in the Act for an administrative proceeding before the Secretary to compel the filing of a "new drug" application or to halt the marketing of a drug for which there is no approval by the Secretary. It is not without significance that, so far as the official reports reflect, the Secretary has never attempted directly to exercise such jurisdiction. The only occasions on which he has sought to assert such jurisdiction has been as an element in his defense to a declara-

tory judgment action.[20] Moreover, when FDA undertook its new responsibilities under the 1962 Amendments, it sought merely to review "the efficacy of *all new drugs that had been cleared*, for safety only, between 1938 and October 10, 1962" (Italics added) and enlisted the services of the National Academy of Sciences—National Research Council for this limited task. It did not assert the right to review, or assume the burden of reviewing, for efficacy, drugs such as those involved here, which had been commercially marketed on the basis of a general recognition of safety without an effective NDA as of the effective date of the 1962 Amendments. It, thus, recognized that its adjudicatory rights extended merely to the approval, or the withdrawal of approval,[22] of a drug embraced in a "new drug" application that had been approved. This confirms the conclusion that the halting of the marketing of a drug, for which there is no NDA, may not be by administrative action but must be by an injunction or *in rem* seizure proceeding, in which the Secretary appears, not in a judicial but in a prosecutorial role.[23] Those are the procedures prescribed and available to the Government under the Act.[24] The

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[20] See, *Hynson, Westcott & Dunning, Inc.* v. *Richardson* (Civ. No. 21112, D. Md., decided 9/16/70); and *Ciba Corp.* v. *Richardson* (Civ. No. 1210-70, D. N.J., decided 3/10/71); but c.f., *Lemmon Pharmacal, supra.*

[21] See *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F.2d 536, 539, and 31 F.R. 9426.

[22] The authority of the Secretary to withdraw an approval of any "new drug" application filed under the Act of 1938 after hearing is specifically granted by Section 355(e), 21 U.S.C.

[23] Of course, in a proper case the Government may also institute criminal proceedings in the District Court. See Section 333, 21 U.S.C.

[24] Cf. *United States* v. *Allan Drug Corporation* (10th Cir. 1966) 357 F.2d 713, 718, cert. den. 385 U. S. 899, in which the Secretary is quoted to the effect that, " 'As to drugs already on the market that have never been subject to the new-drug procedure but are not generally recognized as effective, the burden remains on the

Secretary, it is true, has offered to provide "advice" on whether a product meets the qualification of an old drug but he categorizes his action in such instances as merely "advice" and makes no claim of finality therefor. Nor is there, as we have already observed, any provision for judicial review of such "advice".[25] The only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of an approval, of a "new drug" application.[26] That this is so follows from the limitations placed by the Act on judicial review of the decisions of the Secretary. The Secretary himself asserted, shortly after the enactment of the 1962 Amendments, in *Turkel* v. *Food and Drug Administration, Dept. of H.E.W., supra,* at p. 845, that the Act "grants a right to appeal only from an order of the Food and Drug Administration approving or disapproving a New Drug Application". In keeping with the Secretary's contention as to the extent of his adjudicatory powers, the Court in that case held that the right of appeal from an order of the Secretary "applies only to an order of the Secretary refusing or withdrawing approval of an application for sale and distribution of a new drug" (at pp. 845-6). It is not to be assumed that the Act confers an adjudicatory right on the Secretary from which no judicial review, however limited, is provided or allowed. Yet this is the usual situation that would be presented if the Secretary were held to have jurisdiction to ad-

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Government to prove *in court*, insofar as unchanged labeling claims are concerned, they do not have their claimed effect. If the labeling claims are changed, however, these must be approved under the new-drug procedure.'" (Italics added.)

[25] See *Turkel* v. *Food and Drug Administration, Dept. of H.E.W.* (6th Cir. 1964) 334 F.2d 844, 846, cert. denied 379 U. S. 990, rehearing denied 380 U. S. 927: "The jurisdiction of the United States Courts of Appeal to review administrative acts of federal agencies is wholly dependent upon statute."

[26] Section 355(b), 21 U.S.C.

judicate whether a drug meets the statutory criteria of a "new drug".[27]

The District Court, in finding concurrent jurisdiction, held that "This grant of authority to approve or withhold approval of new drug application, * * * necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which required an approved new drug application for lawful interstate shipment." This reasoning assumes that an application for approval by the Secretary under the Act poses as its initial issue whether the product is a new drug. No such issue is posed by the application. The very filing of the application is a concession and recognition by the applicant-manufacturer that the article is a "new drug"; otherwise, there would be no reason to file the application. As a matter of fact, in the prescribed form of application, the applicant describes his product as "a new drug". 21 C.F.R. 130.4. The applicant makes the determination whether his product is a "new drug" and whether he must file for pre-marketing clearance by the Secretary. And when filed, the application puts in issue only one question: Is the article safe and effective? That and that alone is the issue to be considered by the Secretary in connection with an application for approval filed by a manufacturer under Section 355(d), 21 U.S.C. That issue is quite different from that presented when there is an issue whether a drug fits the statutory definition of "new drug" in the Act. The criterion for ascertaining whether a product is within the statutory definition of "new drug" under the Act is not safety and effectiveness *per se*, which, as we have observed, is the issued before the Secretary in connection with application for approval of a "new drug", but "whether the government has shown by a preponderance of the

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[27] Cf., *Abbott Laboratories* v. *Gardner* (1967) 387 U. S. 136, at p. 140.

evidence that the 'drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof." [28] That is an issue that must be and is resolved, sometimes with, and at other times without a jury, in practically every injunctive, seizure, or criminal proceeding under the Act. See, for instance, *United States* v. *Articles of Drug Labeled "Quick-O-Ver"*, *supra; United States* v. *41 Cases, More or Less* (5th Cir. 1970) 420 F.2d 1126, 1128; *United States* v. *Article of Drug, etc., supra*, at p. 392; *United States* v. *Article . . . Consist. of 216 Carton* (2d Cir. 1969) 409 F.2d 734, 742; *United States Article Consisting of 36 Boxes, etc., supra*, at p. 113; see, also, *United States* v. *Article of Drug, etc.* (D.C. Md. 1971) 331 F. Supp. 912, 915-7. That was one of the issues resolved in the declaratory action of *Lemmon Pharmacal Co.* v. *Richardson, supra.*[29] It is

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[28] *United States* v. *Articles of Drug Labeled "Quick-O-Ver"*, *supra*, at pp. 45-6.

See, also:

AMP, Incorporated v. *Gardner, supra*, at p. 831:

"But the safety of the products is not what is at issue here. The question is whether there is general recognition among qualified experts of the products' safety and effectiveness—if there is not, the products must be submitted to the Secretary of Health, Education and Welfare for a determination as to safety, adequacy of testing, etc."

United States v. *Article of Drug, etc.* (5th Cir. 1969) 415 F.2d 390, 392:

"Both sides agree that the nature of expert opinion about Furestrol, and not its actual safety or effectiveness, is the ultimate fact issue."

Cf., *United States* v. *Seven Cartons, More or Less, etc.* (7th Cir. 1970) 424 F.2d 1364, 1365.

[29] In discussing this case, the commentator in 60 Georgetown Law Journal, p. 199, note 87, says:

[Footnote continued on page 44a]

manifestly a justiciable issue and the plaintiffs are entitled to a judgment on that issue by the Court, which alone has the jurisdiction to resolve it. In the absence of any statutory review proceedings within which they may assert their claim of exemption, the plaintiffs are not to be compelled to proceed at their peril, subject to the possibility of both civil and criminal penalties, but are entitled to seek relief by way of a declaratory judgment action. The District Court should accordingly have retained jurisdiction and proceeded to determine whether the plaintiffs' drugs met the criteria for exemption under Section 107(c)(4). We deem it premature for us to consider at this stage whether plaintiffs' products meet such criteria. That issue was not developed in the record before, or ruled on by, the District Court.[30] Upon remand, the issue can be considered by the Court in the light of the record that may be made by the parties.

REMANDED, WITH DIRECTIONS.

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[29] [Continued]

"In *Lemmon Pharmacal*, the Court, while noting that determining safety and efficacy would normally be within the primary jurisdiction of the agency, concluded that the question of section 107(c)(4) protection was properly before it."

[30] See *United States* v. *Article Consisting of 36 Boxes etc.*, *supra*, at p .113.

APPENDIX C(2)

UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 71-1596

USV PHARMACEUTICAL CORPORATION,
Appellee,

—versus—

ELLIOT L. RICHARDSON, Secretary of Health, Education, and Welfare, and HERBERT L. LEY, JR., Commissioner of Food and Drugs, Food and Drug Administration,
Appellants.

Appeal from the United States District Court for the Eastern District of Virginia, at Alexandria. Oren R. Lewis, District Judge.

(Argued December 8, 1971. Decided May 24, 1972.)

Before WINTER, RUSSELL and FIELD, Circuit Judges.

RUSSELL, CIRCUIT JUDGE:

Unlike the drug manufacturers in *Bentex*,[1] this plaintiff markets a line of citrus bioflavonoid drugs,[2] of

[1] *Bentex Pharmaceuticals, Inc.* v. *Richardson*, No. 71-1243 (4th Cir., appeal docketed March 11, 1971).

[2] "Bioflavonoid" is defined in Dorland's Illustrated Medical Dictionary, 2d Edition, as follows: "a generic term for a group of compounds which are widely distributed in plants and animals and which are concerned with maintenance of a normal state of the walls of small blood vessels." Stipulation of Facts, # 4.

which all but two were covered by NDAs issued at various times in 1955 and 1956. Like the plaintiffs in *Bentex*, however, it seeks by an action for declaratory judgment to secure the benefit of the exemption available under the "grandfather clause" [a] from the enlarged definition of a "new drug" included in the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act of 1938. The defendants, who are the Secretary of Health, Education and Welfare (hereinafter referred to as HEW) and the Commissioner of the Food and Drug Administration (hereafter referred to as Commissioner), urge that jurisdiction should be refused on two grounds: 1. Primary jurisdiction lies with HEW; and 2. Failure to exhaust administrative remedies. They, also, attack the right of the plaintiff to claim the exemption. The District Court sustained jurisdiction and, largely on the basis of a Stipulation of Facts, upheld plaintiff's right to the statutory exemption both for its NDA'd and its non-NDA'd drugs. We reverse.

The threshold question raised by the defendants and overruled by the District Court may be quickly disposed of. Under similar circumstances in *Bentex*, we sustained the right of the District Court to entertain an action for declaratory judgment. We reach the same result here. Since we dismiss the claim of the plaintiff for exemption on behalf of its drugs on substantive grounds, it is unnecessary to consider the additional objection that plaintiff has failed to exhaust administrative remedies.

The substantive issue posed by this action is the right of the plaintiff to the exemption provided by section 107(c)(4) from the revised definition of "new drug" incorporated in the 1962 Amendments. In resolving that issue, we must differentiate, even as the "grandfather

[a] Section 107(c)(4), Pub. L. 87-781 (1962), 21 U.S.C., 1972 Supplement, pp. 191-2.

clause" itself does, between the plaintiff's drugs, which were covered by an "effective NDA",[4] and those, which were marketed without an NDA. The Act makes a distinction in "grandfather" rights between a drug marketed under an NDA[5] and one marketed without an NDA. In the case of a drug covered by a previously approved NDA, the 1962 Amendments required the Secretary to withdraw NDAs if after notice and opportunity of hearing, the applicant failed to file substantial evidence[6] that the drug previously approved is both safe and effective.[7] For such drugs, however, a grace period or temporary "grandfather right" was granted. Under it, the manufacturer was given two years within which to develop his showing of effectiveness and, during this period, the Secretary was prohibited from withdrawing or suspending the previously granted NDA.[8] On the other hand, a non-NDA'd drug which met the criteria stated in section 107(c)(4) was exempted permanently from the amended definition of "new drug" made by the 1962 Amendments and was thereby relieved of securing an approved NDA as a condition for marketing clearance. The statutory criteria for this permanent "grandfather" exemption are stated as "any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined in section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act".

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[4] "Effective", as used in this phrase, means simply approved. Hagan, *Grandfather Protection Under the Drug Amendments of 1962*, 19 Food Drug Cosm. L. J., 119, p. 121.

[5] This is the term used to describe an approved pre-clearance application under Section 355.

[6] "Substantial evidence" is defined in the Act (21 U.S.C. 355(d)).

[7] Section 355(e), 21 U.S.C.

[8] Section 107(c)(3)(B), 21 U.S.C., note foll. Section 321.

It is the contention of the plaintiff that all its drugs in question, both those previously NDA'd and those not, are protected by the permanent "grandfather clause" (i.e., Section 107(c)(4)). Because the statute seemingly makes a distinction between the two, it is proper to consider separately the two groups of drugs: i.e., those having NDAs and those without NDAs.

Taking up first plaintiff's NAD'd drugs: There is no dispute that such drugs met criteria (A) and (B), as set forth in the "grandfather clause", but the defendants seriously dispute the claim that they meet condition (C). Facially at least, this contention of the defendants seems unanswerable. These drugs are "covered by an effective application" or NDA, and are thus specifically barred by condition (C) from qualifying for exemption from the application of the effectiveness Amendments of 1962. The District Court found, however, that before "the day immediately preceding the enactment date", which was October 9, 1962, the previously granted NDAs had been effectively and practically withdrawn and that accordingly the drugs were not covered by an effective NDA on the crucial date of October 9, 1962. The error in this reasoning, however, is that it assumes that a manufacturer may effect a withdrawal of an effective NDA, either by a formal notice or by discontinuing compliance with the reporting requirements for NDA'd drugs. While an applicant may, during the pendency of his application, withdraw his application, he has no such right after approval of the application by the Secretary. At that point only the Secretary can withdraw the approval. As one commentator has accurately summed up, "It is true that a manufacturer may withdraw a pending NDA. Sec. 21 C.F.R. sec. 130.8 (1971). However, no provision in the law permits a manufacturer to withdraw an effective NDA; only the FDA can do so through Section 505(e) procedure".* Prior to October 9, 1962, there was

* Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185 at p. 198, n. 77 (1971).

in this case no proceeding by FDA under Section 505(e) with reference to plaintiff's NDA'd drugs and there was accordingly no valid withdrawal of the plaintiff's effective NDAs, on or before the enactment date of the 1962 Amendments.

The plaintiff, through, presses another theory upon the basis of which it claims the previously issued NDAs are to be regarded as ineffective on October 9, 1962. Thus it argues that its pre-1962 NDA'd drugs became generally recognized as safe on or before October 9, 1962. So much the defendants seem to concede in the Stipulation of Facts submitted to the District Court. From this fact, it reasons that its NDA drugs ceased to be "new drugs" as defined in the Act, on or before October 9, 1962, and, ergo, its previously issued NDAs were no longer needed or "effective" on the critical date of October 9.[10] The difficulty with this argument, plausible thought it may be, is that it would make surplusage of requirement (C) in the statute. Thus, if a drug met the test set up in (B), that is, was generally recognized as safe on October 9, 1962, it would not be necessary, under the plaintiff's argument, to consider whether (C) was applicable or not. Such a construction of the exemption statute, under which a clearly stated condition to its application is to treated as a nullity, offends the well-settled rule of statutory construction that all parts of a statute are to be given effect if at all possible.[11] It is manifestly possible to give effect to the conditions enunciated in both (B) and (C). There are many drugs that satisfy both conditions, that is, are generally recognized as safe and effective and are being marketed without an approved NDA. There is nothing inconsistent in the two require-

[10] See Barth, *Following the NAS-NRC Effectiveness Review, What?*, 22 Business Lawyer, 1185, 1187 (1967).

[11] *Jarecki* v. *G. D. Searle & Co.* (1961) 367 U.S. 303, 307; *Ginsberg & Sons* v. *Popkin* (1932) 285 U.S. 204, 208.

ments. Moreover, condition (C) represented a limitation on the right to an exemption that the Congress clearly and unmistakably intended to apply. The Congress never intended that a drug being marketed under an approved NDA might qualify under the "grandfather clause." This is plain from the comment in the Conference Committee Report that the exemption was to apply "to existing labeling claims of drugs *that have never previously been subject to the new-drug procedure*". (Italics added.) H.R. Rep. 2526, 87th Cong., 2d Sess., p. 23. Moreover, the argument of the plaintiff would run counter to the principle that statutory exemptions, particularly as applied to statutes concerned with public health and safety, are to be strictly and narrowly construed.[12]

The plaintiff has, however, two drugs,[13] involved in this proceeding, which were generally recognized as safe and were [14] marketed as "old drugs" without an approved NDA on October 9, 1962. These drugs, as we earlier indicated, present separate problems from those drugs for which there are approved NDAs. They fall into the category of what are generally described in the trade as "me-too" drugs.[15] Such a drug, if generally regarded as safe on October 9, 1962, meets literally the criteria for exemption stated in the "grandfather clause". To sustain the exemption, however, creates an inequitable result, provided the pioneer drug was NDA'd. In that event, the pioneer drug would be subject to withdrawal of marketing privilege absent substantial evidence of effec-

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[12] *United States* v. *Allan Drug Corporation* (10th Cir. 1966) 357 F.2d 713, 718, cert. denied 385 U.S. 899.

[13] Duo-C.V.P. with Vitamin K Capsules and Bivam.

[14] Stipulation of Facts, Number 17.

[15] A "me-too" drug is generally defined as "one which is equivalent to another, pioneer drug, which preceeded it on the market." Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 198, n. 78, (1971).

tiveness, whereas its copy would enjoy immunity from any such requirement under Section 107(c)(4). Most commentators, while admitting the incongruity of this result, justify it as one compelled by the literal language of the statute.[16] Their reasoning is similar to that of the Court in *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 542, where speaking to a somewhat illogical provision in this same Act, Judge Friendly said: "A sufficient answer is the simple if not altogether satisfying one that Congress said so."[17] The FDA itself has recognized the vexing problem presented by the "me-too" drug and has sought to resolve it by a change in its position on the scope and application of an NDA.

It is the contention of the FDA that an approved NDA covers not merely the marketing of the parent but also its "me-too" offsprings and for that reason the "me-too" drugs have been permitted to be marketed without an NDA. Accordingly, under this theory, the withdrawal of the approved NDA of the pioneer operates as a withdrawal of marketing rights for the "me-too", unless the latter, either individually or in conjunction with its pioneer, provides substantial evidence of effectiveness. This view has, however, been severely criticized and with considerable reason. It is, as one critic has observed, "at variance with the uniform position it (FDA)

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[16] See, Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 203 (1971):

> "Surely, me-too drugs never processed through the new drug procedures satisfy all the requirements of section 107(c)(4)."

To the same effect is Hagan, *Grandfather Protection Under the Drug Amendments of 1962*, 19 Food Drug Cosm. L.J., 119, at pp. 125-6; *D'Andrade, The Effect of NAS-NRC Review on Me-Too and Post-'62 Drugs*, 25 Food, Drug, Cosm. L.J., 330, 334 (1970).

[17] This, of course, is not the only inequity in the Amendments. There are other inequities, as FDA freely conceded at a House Hearing before a Subcommittee of the Commission on Government Operations on Drug Efficacy, Part 2, 91st Con., 1st Sess. (1969), pp. 384-5.

has taken over the years with regard to the nature of NDAs." This position, which is termed the "personal approach" holds that "Section 505 applies to drugs as individual articles, not as collective groups, and that each manufacturer of a new drug must file his own NDA." This critic concludes with the observation that it is "an unjustifiable exercise in semantics to say that a drug legally marketed without an NDA was 'covered' by the NDA of another manufacturer's drug." [18]

That the policy of FDA has heretofore been contrary to the position now taken by it is further illustrated by the circumstances under which at least one of the "me-toos" of the plaintiff began marketing. Prior to marketing Bivam, one of its "me-toos" similar in formula to other drugs previously NDA'd by it, the plaintiff inquired of FDA whether it was an "old drug" entitled to be marketed without an NDA. FDA, after reviewing its composition and labeling, advised the plaintiff it was a product "generally regarded as safe" (and thus an "old drug") and could be marketed without an NDA. There was no suggestion by the plaintiff that it sought to market this drug under any previous NDA granted one of its products nor did the FDA base its advice on that basis. Both the plaintiff and FDA assumed at that time that a "me-too" drug, which had become generally recognized as safe, was entitled to be marketed without an NDA; in short, that the qualification for marketing a "me-too" drug was general recognition of safety and not the NDA of its pioneer.

It would seem that the consistent construction of the Act by the FDA for thirty years [19] and a construction

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[18] Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 203, n. 111 (1971).

[19] See, Hagan, *supra*, at p. 125:

> "Furthermore, the concept that new drug clearance by one manufacturer affects the rights of subsequent manufacturers

which accords with the literal language of the Act itself may only be changed by Congress itself.[20] In fact, the General Counsel of FDA, in testimony before a House Subcommittee Hearing on Drug Efficacy, Part 2 (91st Cong., 1st Sess., 1969) p. 375, expressed the wish that Congress would "pass" a clarifying amendment on this issue, conceding that the position of his agency was in considerable doubt.

But even if it be assumed that "me-too" drugs are generally entitled to section 107(c)(4) protection, provided they were generally recognized as safe on October 9, 1962, that does not resolve the right of the plaintiff's "me-toos" to exemption. As has been pointed out, the reasoning on which "me-toos" are regarded as not covered by the NDAs granted the manufacturers of their pioneers is that an NDA is regarded as "personal" to the manufacturer submitting the application and to the drug covered. But in this case, the "me-toos" are similar in formula and labeling to other drugs for which the plaintiff itself applied and obtained NDAs. It is true that, in the case of one drug at least, to which reference has already been made, plaintiff's "me-toos" were regarded as exempt, not because plaintiff had an approved NDA for a similar drug, but because FDA was of the opinion that it met the requirements for classification as an old drug. Nonetheless, it is the "per-

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is inconsistent with the established doctrine that new drug clearance is *personal* to the applicant, and does not embrace the drug *per se*."

[20] Cf., comment in Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal 185, at pp. 206-7 (1971):

"Ultimately the issue of the status of me-too drugs will have to be squarely faced, and the FDA interpretation of section 107 (c)(4), holding that they follow the pioneer's fate, should be repudiated by the courts. In that event the agency will undoubtedly ask Congress for new legislation to remedy the situation. In view of the obvious inequities in the present situation, this would seem to be the most desirable solution."

sonal" character of the NDA that has been deemed as the basis on which it is contended that the "me-toos" are not covered by the NDA granted another manufacturer, albeit the drugs involved may be similar. That reasoning manifestly cannot sustain a right of exemption in favor of plaintiff's "me-toos". The plaintiff's NDAs, being "personal" to it, would cover all its products similar in formula, including those specifically described in its applications and all others like in formula. The similarity in formula, between plaintiff's NDA'd drugs and its "me-toos" is stipulated. Under those circumstances, both the NDA'd and the "me-too" drugs will be treated alike and neither can qualify for exemption under the terms of section 107(c)(4). It is recognized that this conclusion places the plaintiff in a less favorable position than that occupied by others who may have copied its product prior to October 9, 1962. That inequity is, however, inherent in the law and may only be redressed by Congress, not by the Courts under the guise of construction.

Reversed, with directions to enter judgment for the defendants.

REVERSED.

APPENDIX D

Conflicting Opinion

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 71-1512

CIBA CORPORATION, a corporation of the State of Delaware,

Appellant,

v.

ELLIOTT L. RICHARDSON, Secretary of Health, Education & Welfare, and DR. CHARLES C. EDWARDS, Commissioner of Food and Drugs.

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Argued April 11, 1972
Before HASTE, VAN DUSEN and ALDISERT, *Circuit Judges*

OPINION OF THE COURT
(Filed June 5, 1972)

PER CURIAM:

Ciba Corporation has taken this appeal from an order of the District Court for the District of New Jersey dismissing a complaint in which Ciba sought a declaratory determination that its drug product, Ritonic Capsules, is exempt from the requirement of 1962 amendments of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355,

that new drugs be excluded from the market unless proven effective as claimed for them. The complaint also sought an injunction against the implementation of an administrative order, entered by the Commissioner of Food and Drugs after notice and opportunity for an evidentiary hearing, that withdrew approval of the drug upon the basis of a finding that the manufacturer's claims as to its effectiveness were unproven. On appeal, the Court of Appeals for the Second Circuit has affirmed that order. *Ciba-Geigy Corp.* v. *Richardson*, 1971, 446 F.2d 466. That affirmance occurred after the district court had dismissed the present suit and is subject to review by the Supreme Court.

The appellant's basic position seems to be that neither the Commissioner in an administrative proceeding under § 355(e) to determine whether lack of effectiveness as claimed makes a drug unmarketable, nor a court of appeals in reviewing the administrative decision, has jurisdiction to decide as to threshold question whether the product in controversy is a "new drug" within the meaning of the statute, § 355, that covers "new drug" applications and administrative proceedings pursuant thereto. We find no merit in that argument. Inherent in the grant of administrative competency to conduct and decide new drug proceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such a proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision.

In disapproving Ritonic Capsules the Commissioner and the Court of Appeals for the Second Circuit necessarily decided that the 1962 amendments of the Act were applicable to that product. That determination is reviewable by the Supreme Court. It is neither necessary nor appropriate that the District Court for the District of

New Jersey entertain a separate suit by the loser in the administrative proceeding and in the direct appeal therefrom for a redetermination of the same question.

The judgment will be affirmed.

A True Copy:
Teste:

Clerk of the United States Court of Appeals for the Third Circuit.